

When given intravenously, phenoxybenzamine hydrochloride should always be diluted and given by infusion. Intravenous fluids must always be given beforehand to ensure an adequate circulating blood volume and to prevent a precipitous fall in blood pressure. Care should be taken to avoid extravasation. Contamination of the skin should also be avoided since contact sensitisation may occur.

Porphyria. Phenoxybenzamine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Since phenoxybenzamine only blocks alpha receptors, leaving the beta receptors unopposed, use with drugs such as adrenaline that also stimulate beta receptors may enhance the cardiac-accelerating and hypotensive action of phenoxybenzamine.

Pharmacokinetics

Phenoxybenzamine is incompletely and variably absorbed from the gastrointestinal tract. After oral dosage the onset of action is gradual over several hours and persists for 3 or 4 days following a single dose. The maximum effect is attained in about 1 hour after an intravenous dose. The plasma half-life after intravenous dosage is about 24 hours. Phenoxybenzamine is metabolised in the liver and excreted in the urine and bile, but small amounts remain in the body for several days. The duration of action is thought to depend on the rate of synthesis of new alpha receptors following irreversible covalent bonding to existing alpha receptors by a reactive intermediate of phenoxybenzamine.

Uses and Administration

Phenoxybenzamine is a powerful alpha-adrenoceptor blocker (p.1153) with a prolonged duration of action; it binds covalently to alpha receptors in smooth muscle to produce an irreversible ('non-competitive') blockade. A single large dose of phenoxybenzamine can cause alpha-adrenoceptor blockade for 3 days or longer.

Phenoxybenzamine is used in the management of phaeochromocytoma (p.1179). It has also been employed in severe shock (p.1183) and in the treatment of urinary retention (p.2180).

Phenoxybenzamine is used as the hydrochloride. It is given orally or by intravenous infusion as a dilute solution.

In **phaeochromocytoma** it is used to control the hypertension associated with excessive catecholamine release during the pre-operative period and in patients whose tumours are inoperable. A beta blocker may also be given to control tachycardia, but not before alpha blockade has completely suppressed the pressor effects of the phaeochromocytoma. The usual initial oral dose of phenoxybenzamine hydrochloride is 10 mg once or twice daily, increased gradually, according to the patient's response, to a usual dose of 1 to 2 mg/kg daily in 2 divided doses. It may be given intravenously for operative cover in patients with phaeochromocytoma in a daily dose of 1 mg/kg in 200 mL of sodium chloride 0.9% infused over at least 2 hours. A similar intravenous dose in 200 to 500 mL of sodium chloride 0.9% has been given in the management of severe **shock**.

For **urinary retention** due to neurogenic bladder an oral dose of 10 mg twice daily has been given.

Preparations

BP 2008: Phenoxybenzamine Capsules;
USP 31: Phenoxybenzamine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Dibenylene; **Austria:** Dibenzyran; **Ger.:** Dibenzyran; **Gr.:** Dibenylene; **Hong Kong:** Dibenylene; **India:** Fenoxene; **Israel:** Dibenylene; **Neth.:** Dibenylene; **NZ:** Dibenylene; **S.Afr.:** Dibenylene; **UK:** Dibenylene; **USA:** Dibenylene.

Phenprocoumon (BAN, USAN, rINN)

Fenprocumón; Fenprocumon; Fenprokumon; Fenprokumoni; Phenprocoumonone; Phenprocoumonum; Phenylpropylhydroxycoumarin. 4-Hydroxy-3-(1-phenylpropyl)coumarin.

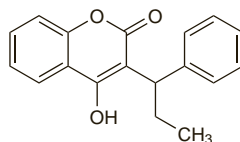
Фенпрокумон

$C_{18}H_{16}O_3 = 280.3$.

CAS — 435-97-2.

ATC — B01AA04.

ATC Vet — QB01AA04.



Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p.1425.

Effects on the liver. A woman who had twice previously developed jaundice while taking phenprocoumon developed jaundice and parenchymal liver damage when, after some years, phenprocoumon was again given.¹ Other cases of phenprocoumon-associated liver damage have been reported.²⁻⁴

1. den Boer W, Loeliger EA. Phenprocoumon-induced jaundice. *Lancet* 1976; **i**: 912.
2. Slagboom G, Loeliger EA. Coumarin-associated hepatitis: report of two cases. *Arch Intern Med* 1980; **140**: 1028-9.
3. Cordes A, et al. Phenprocoumon-induziertes Leberversagen. *Dtsch Med Wochenschr* 2003; **128**: 1884-6.
4. Bulang T, et al. Akutes Leberversagen durch Phenprocoumon—drei Fallberichte. *Z Gastroenterol* 2004; **42**: 1055-8.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p.1427). Specific references to interactions involving phenprocoumon can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antidepressants; antidiabetics; antitumor drugs; antineoplastics; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenprocoumon is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Metabolism is mediated partly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. The half-life is 5 to 6 days. It is excreted in the urine and faeces as conjugated hydroxy metabolites and parent compound. Phenprocoumon is given as a racemic mixture; the *S*-isomer is more potent. The stereoisomers have different pharmacokinetics.

References

1. Husted S, Andreasen F. Individual variation in the response to phenprocoumon. *Eur J Clin Pharmacol* 1977; **11**: 351-8.
2. Toon S, et al. Metabolic fate of phenprocoumon in humans. *J Pharm Sci* 1985; **74**: 1037-40.
3. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44**: 1227-46.

Uses and Administration

Phenprocoumon is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187). Initial doses are up to 9 mg on the first day followed by 6 mg on the second day. Maintenance doses are usually from 1.5 to 6 mg daily, depending on the response.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Marcoumar; **Belg.:** Marcoumar; **Braz.:** Marcoumar; **Denm.:** Marcoumar; **Ger.:** Falithrom; Marcumar; marcuphen; Phenpro; Phenprogamma; **Neth.:** Marcoumar; **Switz.:** Marcoumar.

Phentolamine Mesilate (BANM, rINNM)

Fentolamiinimesilaatti; Fentolamin mesylát; Fentolaminmesilat; Fentolamin-mesilát; Fentolamin mesilas; Mesilato de fentolamina; Phentolamine, mesilate de; Phentolamine Mesylate; Phentolamine Methanesulphonate; Phentolamini mesilas. 3-[N-(2-Imidazolin-2-ylmethyl)-p-toluidino]phenol methanesulphonate.

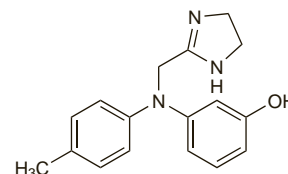
Фентоламина Мезилат

$C_{17}H_{19}N_3O_3 \cdot CH_3SO_3 = 377.5$.

CAS — 50-60-2 (phentolamine); 73-05-2 (phentolamine hydrochloride); 65-28-1 (phentolamine mesilate).

ATC — C04AB01; G04BE05.

ATC Vet — QC04AB01; QG04BE05.



(phentolamine)

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

Ph. Eur. 6.2 (Phentolamine Mesilate). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Phentolamine Mesilate). A white or off-white, odourless crystalline powder. Soluble 1 in 1 of water, 1 in 4 of alcohol, and 1 in 700 of chloroform. Its solutions in water have a pH of about 5 and slowly deteriorate. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Treatment

The adverse effects of phentolamine are primarily due to its alpha-adrenoceptor blocking activity and include orthostatic hypotension and tachycardia. Myocardial infarction and cerebrovascular spasm or occlusion have been reported occasionally, usually in association with marked hypotension; flushing, sweating, and feelings of apprehension may accompany hypotensive episodes. Angular pain and arrhythmias have been reported rarely. Nausea, vomiting, and diarrhoea may also occur. Other side-effects include weakness, dizziness, flushing, and nasal congestion. Hypoglycaemia has been reported following overdose.

Severe hypotension may occur in overdose although phentolamine has a short duration of action. Treatment may include support of the circulation by postural measures and parenteral fluid volume replacement. Noradrenaline may be given cautiously to overcome alpha-adrenoceptor blockade. Adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia.

When injected into the corpus cavernosum of the penis phentolamine has been associated with local pain; induration and fibrosis may occur with repeated use. Priapism has occurred.

Precautions

Phentolamine should not generally be given to patients with angina pectoris or other evidence of ischaemic heart disease. Care should be taken in patients with peptic ulcer disease, which may be exacerbated.

Interactions

Since phentolamine only blocks alpha receptors, use with drugs such as adrenaline may lead to severe hypotension and tachycardia due to unopposed beta-adrenoceptor stimulation.

Pharmacokinetics

After intravenous dosage, the half-life of phentolamine has been reported to be 19 minutes. It is extensively metabolised and about 13% of an intravenous dose is excreted unchanged in the urine.

Uses and Administration

Phentolamine is an alpha-adrenoceptor blocker (p.1153) which also has a direct action on vascular smooth muscle. It produces vasodilatation, an increase in cardiac output, and has a positive inotropic effect, but is reported to have little effect on the blood pressure of patients with essential hypertension. The alpha-receptor blocking action is reversible ('competitive') and non-selective, and the duration of effect is relatively short.

Phentolamine is given in the management of hypertensive crises, particularly those due to excessive catecholamine release associated with surgery for pheochromocytoma (p.1179). It has been used for the differential diagnosis of pheochromocytoma, but has largely been superseded by estimations of catecholamines in blood and urine.

Phentolamine is also used to prevent or treat dermal necrosis and sloughing associated with the intravenous infusion or extravasation of noradrenaline. It has been used in the treatment of erectile dysfunction (p.2179).

Phentolamine is given by injection as the mesilate.

In patients with hypertensive crises during surgery for **pheochromocytoma**, a dose of 2 to 5 mg of phentolamine mesilate is given intravenously and repeated if necessary; blood pressure should be monitored. A dose of 1 mg intravenously is used for children. The intramuscular route may be used pre-operatively and for diagnostic procedures.

For prevention of **dermal necrosis** during intravenous infusion of noradrenaline, 10 mg of phentolamine mesilate is added to each litre of solution containing noradrenaline. For treatment of extravasation of noradrenaline, 5 to 10 mg of phentolamine mesilate in 10 mL of sodium chloride 0.9% is injected into the affected area.

For **erectile dysfunction**, phentolamine mesilate is given by injection into the corpora cavernosa of the penis. It is usually given with papaverine, but a preparation containing phentolamine with aviptadil (vasoactive intestinal peptide) may also be used. Phentolamine has also been tried orally.

Hyperhidrosis. Hyperhidrosis (p.1580) is usually treated with topical aluminium salts or topical antimuscarinics, but intradermal botulinum A toxin or procedures such as endoscopic transthoracic sympathectomy may be needed in severe cases. Phentolamine has been tried as an alternative. Improvement in symptoms has been reported¹ in 2 patients with generalised hyperhidrosis given 100 mg of phentolamine mesilate by intravenous infusion over 6 hours. Improvement lasted for 2 to 3 months and the infusion was repeated, in 1 patient several times.

1. McCleane G. The use of intravenous phentolamine mesilate in the treatment of hyperhidrosis. *Br J Dermatol* 2002; **146**: 533-4.

Pain. Sympathetic nerve block (p.1853) is used in a number of pain syndromes and usually involves injection of local anaesthetics. Phentolamine has been used as an alternative and beneficial results have been reported in pain associated with chronic pancreatitis,¹ pancreatic and other visceral cancers,^{2,3} and chronic gastroparesis.⁴

Complete resolution of pain has also been reported in 2 patients with cutaneous leiomyomata given oral doxazosin.⁵

1. McCleane GJ. Phentolamine abolishes the pain of chronic pancreatitis. *Br J Hosp Med* 1996; **55**: 521.

2. McCleane GJ. Intravenous phentolamine mesilate alleviates the pain of pancreatic carcinoma. *Pain* 1997; **73**: 263-4.

3. Yasukawa M, *et al.* Intravenous phentolamine infusion alleviates the pain of abdominal visceral cancer, including pancreatic carcinoma. *J Anesth* 2007; **21**: 420-3.

4. Phillips WJ, *et al.* Relief of acute pain in chronic idiopathic gastroparesis with intravenous phentolamine. *Ann Pharmacother* 2006; **40**: 2032-6.

5. Batchelor RJ, *et al.* Successful treatment of pain in two patients with cutaneous leiomyomata with the oral alpha-1 adrenoceptor antagonist, doxazosin. *Br J Dermatol* 2004; **150**: 775-6.

Preparations

BP 2008: Phentolamine Injection;

USP 31: Phentolamine Mesylate for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Regitina; **Austral.:** Regitine; **Belg.:** Regitine; **Braz.:** Herivyl; Regitina†; Vigamed; **Canad.:** Rogitine; **Dennm.:** Regitin; **Gr.:** Regitine; Rogitine†; **Hung.:** Regitine; **Israel:** Regitine; **Mex.:** Z-Max†; **Neth.:** Regitine; **NZ:** Invicorp; Regitine; **S.Afr.:** Regitine†; **Switz.:** Regitine; **UK:** Rogitine; **USA:** Regitine†; **Venez.:** Regitina†.

Multi-ingredient: **Austria:** Androskat; **Neth.:** Androskat; **USA:** Tri-Mix.

Pholedrine Sulfate (rINN) ⊗

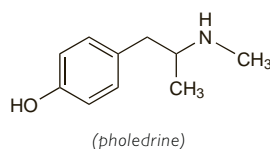
Isodrine Sulphate; Pholédrine, Sulfate de; Pholedrine Sulphate (BANM); Pholedrini Sulfas; Sulfato de foledrina; Sympropanaminum (pholedrine); 4-(2-Methylaminopropyl)phenol sulfate.

Фоледрина Сульфат

(C₁₀H₁₅NO)₂·H₂SO₄ = 428.5.

CAS — 370-14-9 (pholedrine); 6114-26-7 (pholedrine sulfate).

The symbol † denotes a preparation no longer actively marketed



Profile

Pholedrine is a sympathomimetic (p.1407) used in the treatment of hypotensive states. It is usually given orally as the sulfate, often in combination with other drugs, and has also been included in preparations promoted for vascular disorders. Pholedrine eye drops have been used as an alternative to hydroxyamfetamine (p.2322) in the diagnosis of Horner's syndrome.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Ger.:** Adyston†; Zellaforte N Plus†; **Switz.:** Ortho-Maren retard.

Picotamide (BAN)

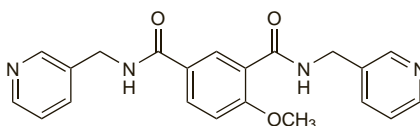
G-137; Picotamida; Picotamide, monohydrate de; Picotamid-monohidrat; Picotamidum monohydricum; Pikotamid monohydrat; Pikotamidmonohydratt; Pikotamidmonohydrat; Pikotamido monohidrat. 4-Methoxy-N,N'-bis(3-pyridinylmethyl)-1,3-benzenedicarboxamide monohydrate.

C₂₁H₂₀N₄O₃·H₂O = 394.4.

CAS — 32828-81-2 (anhydrous picotamide); 80530-63-8 (picotamide monohydrate).

ATC — B01AC03.

ATC Vet — QB01AC03.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Picotamide Monohydrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water; soluble in dehydrated alcohol and in dichloromethane; dissolves in dilute mineral acids.

Profile

Picotamide is a thromboxane synthase inhibitor and thromboxane receptor antagonist with antiplatelet activity. It is given by mouth in thromboembolic disorders (p.1187) in initial doses of 900 to 1200 mg daily in divided doses, reducing to a maintenance dose of 300 to 600 mg daily.

ACE inhibitor-induced cough. Cough is a recognised adverse effect of ACE inhibitors and has been treated with a number of drugs (see p.1194). Picotamide led to the disappearance of cough in 8 of 9 patients receiving enalapril for hypertension,¹ suggesting that thromboxanes may be involved in the aetiology of ACE inhibitor-induced cough.

1. Malini PL, *et al.* Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. *Lancet* 1997; **350**: 15-18.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Plactidil.

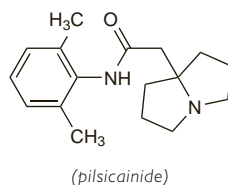
Pilsicainide Hydrochloride (rINN)

Hydrocloruro de pilsicainida; Pilsicainide, Chlorhydrate de; Pilsicainidi Hydrochloridum; SUN-1165. Tetrahydro-1H-pyrrolizine-7a(5H)-aceto-2',6'-xylidide hydrochloride.

Пильсикаинида Гидрохлорида

C₁₇H₂₄N₂O₂·HCl = 308.8.

CAS — 88069-67-4 (pilsicainide); 88069-49-2 (pilsicainide hydrochloride).



Profile

Pilsicainide hydrochloride is an antiarrhythmic with class Ic activity (p.1153).

References.

1. Takabatake T, *et al.* Pharmacokinetics of SUN 1165, a new antiarrhythmic agent, in renal dysfunction. *Eur J Clin Pharmacol* 1991; **40**: 411-14.
2. Okishige K, *et al.* Pilsicainide for conversion and maintenance of sinus rhythm in chronic atrial fibrillation: a placebo-controlled, multicenter study. *Am Heart J* 2000; **140**: 437-44.
3. Kumagai K, *et al.* Single oral administration of pilsicainide versus infusion of disopyramide for termination of paroxysmal atrial fibrillation: a multicenter trial. *Pacing Clin Electrophysiol* 2000; **23**: 1880-2.
4. Ogawa R, *et al.* Population pharmacokinetic and pharmacodynamic analysis of a class IC antiarrhythmic, pilsicainide, in patients with cardiac arrhythmias. *J Clin Pharmacol* 2006; **46**: 59-68.
5. Kumagai K, *et al.* Pilsicainide for atrial fibrillation. *Drugs* 2006; **66**: 2067-73.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Sunrhythm.

Pimobendan (BAN, USAN, rINN)

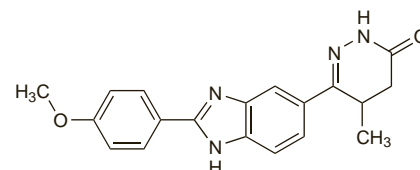
Pimobendaani; Pimobendán; Pimobendanas; Pimobendane; Pimobendanum; UDCG-115. 4,5-Dihydro-6-[2-(p-methoxyphenyl)-5-benzimidazolyl]-5-methyl-3(2H)-pyridazinone.

Пимобендан

C₁₉H₁₈N₄O₂ = 334.4.

CAS — 74150-27-9; 118428-36-7.

ATC Vet — QC01CE90.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Pimobendan). A white or slightly yellowish, hygroscopic powder. Practically insoluble in water; slightly soluble in acetone and in methyl alcohol; freely soluble in dimethylformamide. Store in airtight containers.

Profile

Pimobendan is a phosphodiesterase inhibitor with calcium-sensitising properties. It has positive inotropic and vasodilator activity and is used as an adjunct to standard therapy in the management of heart failure (p.1165). It is given orally in a dose of 1.25 to 2.5 mg twice daily.

Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate.

References.

1. Przechera M, *et al.* Pharmacokinetic profile and tolerability of pimobendan in patients with terminal renal insufficiency. *Eur J Clin Pharmacol* 1991; **40**: 107-11.
2. The Pimobendan in Congestive Heart Failure (PICO) Investigators. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 1996; **76**: 223-31.
3. Yoshikawa T, *et al.* Effectiveness of carvedilol alone versus carvedilol + pimobendan for severe congestive heart failure. *Am J Cardiol* 2000; **85**: 1495-7.
4. The EPOCH Study Group. Effects of pimobendan on adverse cardiac events and physical activities in patients with mild to moderate chronic heart failure: the effects of pimobendan on chronic heart failure study (EPOCH study). *Circ J* 2002; **66**: 149-57.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Acardi.

Pinacidil (USAN, rINN)

P-1134; Pinacidilum; Pinasidiili. (±)-2-Cyano-1-(4-pyridyl)-3-(1,2,2-trimethylpropyl)guanidine.

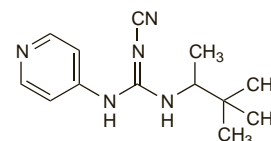
Пинацидил

C₁₃H₁₉N₅ = 245.3.

CAS — 60560-33-0 (anhydrous pinacidil); 85371-64-8 (pinacidil monohydrate).

ATC — C02DG01.

ATC Vet — QC02DG01.



The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)