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.

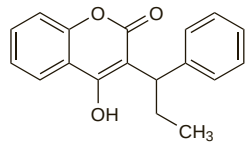
Proprietary Preparations (details are given in Part 3)
Austral.: Dibenyline; ***Austria:*** Dibenzyran; ***Ger.:*** Dibenzyran; ***Gr.:*** Dibenyline; ***Hong Kong:*** Dibenyline; ***India:*** Fenoxene; ***Israel:*** Dibenyline; ***Neth.:*** Dibenyline; ***NZ:*** Dibenyline; ***S.Afr.:*** Dibenyline; ***UK:*** Dibenyline; ***USA:*** Dibenzyline.

Phenprocoumon *(BAN, USAN, rINN)*

Fenprocomón; Fenprocumon; Fenprokumon; Fenprokumoni; Phenprocoumone; 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; antigout 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.

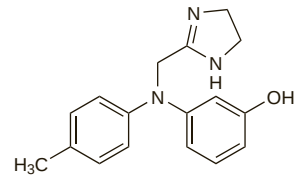
Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Marcoumar; ***Belg.:*** Marcoumar; ***Braz.:*** Marcoumar; ***Denm.:*** Marcoumar; ***Ger.:*** Falithrom; Marcumar; marcuphen; Phenpro; Phenprogamma; ***Neth.:*** Marcoumar; ***Switz.:*** Marcoumar.

Phentolamine Mesilate *(BANM, rINNM)*

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

Фентоламина Мезилат

$C_{17}H_{19}N_3O,CH_4SO_3$ = 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 Mesylate). 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. Anginal 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 overdosage.

Severe hypotension may occur in overdosage 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.