have been reported in some of these studies, the place of pentoxifylline in the overall management of these disorders remains to be established.

1. Akriviadis E, *et al.* Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119:** 1637–48.
2. Skudicky D, *et al.* Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study. *Circulation* 2001; **103:** 1083–8.
3. Di Perri, *et al.* Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. *J Infect Dis* 1995; **171:** 1317–22.
4. Looareesuwan S, *et al.* Pentoxifylline as an ancillary treatment for severe falciparum malaria in Thailand. *Am J Trop Med Hyg* 1998; **58:** 348–53.
5. Navarro JF, *et al.* Urinary protein excretion and serum tumor necrosis factor in diabetic patients with advanced renal failure: effects of pentoxifylline administration. *Am J Kidney Dis* 1999; **33:** 458–63.
6. Lessa HA, *et al.* Successful treatment of refractory mucosal leishmaniasis with pentoxifylline plus antimony. *Am J Trop Med Hyg* 2001; **65:** 87–9.
7. Machado PRL, *et al.* Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. *Clin Infect Dis* 2007; **44:** 788–93.
8. Nery JAC, *et al.* The use of pentoxifylline in the treatment of type 2 reactional episodes in leprosy. *Indian J Lepr* 2000; **72:** 457–67.
9. Dawlah ZM, *et al.* A phase 2 open trial of pentoxifylline for the treatment of leprosy reactions. *Int J Lepr Other Mycobact Dis* 2002; **70:** 38–43.
10. Ducloux D, *et al.* Use of pentoxifylline in membranous nephropathy. *Lancet* 2001; **357:** 1672–3.
11. Okunieff P, *et al.* Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol* 2004; **22:** 2207–13.
12. Chiao TB, Lee AJ. Role of pentoxifylline and vitamin E in attenuation of radiation-induced fibrosis. *Ann Pharmacother* 2005; **39:** 516–22.
13. Delanian S, *et al.* Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol* 2005; **23:** 8570–9.
14. Staubach K-H, *et al.* Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study. *Arch Surg* 1998; **133:** 94–100.
15. Pizarro A, *et al.* Treatment of recurrent aphthous stomatitis with pentoxifylline. *Br J Dermatol* 1995; **133:** 659–60.
16. Chandrasekhar J, *et al.* Oxypentifylline in the management of recurrent aphthous oral ulcers: an open clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87:** 564–7.
17. Thornhill MH, *et al.* A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* 2007; **143:** 463–70.
18. Hisamatsu T, *et al.* Combination therapy including pentoxifylline for entero-Behçet's disease. *Bull Tokyo Dent Coll* 2001; **42:** 169–76.
19. Noel C, *et al.* Immunomodulatory effect of pentoxifylline during human allograft rejection: involvement of tumor necrosis factor α and adhesion molecules. *Transplantation* 2000; **69:** 1102–7.
20. Shu K-H, *et al.* Effect of pentoxifylline on graft function of renal transplant recipients complicated with chronic allograft nephropathy. *Clin Nephrol* 2007; **67:** 157–63.

Venous leg ulcers. A systematic review[1] of pentoxifylline used in the treatment of venous leg ulcers (p.1585) concluded that it was an effective adjunct to compression bandaging, and may be effective alone.

1. Jull A, *et al.* Pentoxifylline for treating venous leg ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 08/05/08).

Preparations

USP 31: Pentoxifylline Extended-Release Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dospan Pento; Pentolab; Previscan; Tamixol; Trental; ***Austral.:*** Trental; ***Austria:*** Haemodyn; Pentohexal; Pentomer; Pentoxi; Pentoximed; Trental; Vasonit; ***Belg.:*** Torental; ***Braz.:*** Arteron; Chemopent†; Pentox; Pentral; Perental†; Peripan; Prodoxifilina; Trental; Vascer; ***Canad.:*** Trental; ***Chile:*** Trental; ***Cz.:*** Agapurin; Pentilin; Pentohexal†; Pentomer; Rentylin†; Trental; Vasonit; ***Denm.:*** Trental; ***Fin.:*** Artal; Pentoxin; Trental; ***Fr.:*** Hatial†; Pentoflux; Torental; ***Ger.:*** Agapurin; Azupentat†; Claudicat; durapental†; Pento; Pento-Puren; Pentohexal; Pentox; Pentoxy†; Ralofekt; Rentylin; Trental; ***Gr.:*** Taronal; ***Hong Kong:*** Pentong; Trenlin; Trental; ***Hung.:*** Angiopurin†; Chinotal; Pentoxyl-EP; Trental; ***India:*** Kinetal; Trental; ***Indon.:*** Erytral; Lentrin; Pentoxifillene; Platof; Reotal; Tarontal; Tioxad; Trenat; Trenfyl; Trental; Trentox; Trenxy; ***Irl.:*** Trental; ***Israel:*** Oxopurin; Trental; ***Ital.:*** Trental; ***Malaysia:*** Trenlin; Trental; ***Mex.:*** Artelife; Eurotofi; Fixoten; Kentadin; Pensiral; Peridane; Profiben; Sufisal; Trental; Vantoxyl; Vasofyl; Vaxolem; Xipen; ***Neth.:*** Trental; ***Norw.:*** Trental; ***NZ:*** Trental; ***Philipp.:*** C-Vex; Pentox; Trental; ***Pol.:*** Agapurin; Apo-Pentox; Dartelin; Pentilin; Pentohexal; Polfilin; Trental; ***Port.:*** Claudicat; Trental; ***Rus.:*** Flexital (Флекситал); Mellinorm (Меллинорм); Pentilin (Пентилин); Trental (Трентал 400); Vasonit (Вазонит); ***S.Afr.:*** Trental; ***Singapore:*** Agapurin†; Trenlin; Trental; ***Spain:*** Elorgan; Hemovas; Nelorpin; Retimax; ***Switz.:*** Dinostral†; Pentoxi; Trental; ***Thai.:*** Agapurin; Elastab; Flexital; Herden†; Penlol; Sipental; Trental; Trepal; ***Turk.:*** Pentox; Trental; Trentilin; Vasoplan; ***UK:*** Neotren; Trental; ***USA:*** Trental; ***Venez.:*** Agapurin; Trental.

Multi-ingredient: ***Arg.:*** Ikatral Periferico.

Perhexiline Maleate *(BANM, USAN, rINNM)*

Maleato de perhexilina; Perhexiline, Maléate de; Perhexilini Maleas; WSM-3978G. 2-(2,2-Dicyclohexylethyl)piperidine hydrogen maleate.

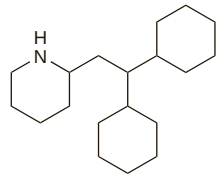
Пергексиллина Малеат

$C_{19}H_{35}N,C_4H_4O_4$ = 393.6.

CAS — 6621-47-2 (perhexiline); 6724-53-4 (perhexiline maleate).

ATC — C08EX02.

ATC Vet — QC08EX02.



(perhexiline)

Profile

Perhexiline maleate may be used in the long-term management of severe angina pectoris (p.1157) in patients who have not responded to other anti-anginal drugs. Its mode of action is complex.

The usual initial oral dose is 100 mg daily, subsequently either increased or decreased, as necessary, at intervals of 2 to 4 weeks; it is generally recommended not to give more than 300 mg daily although doses of 400 mg daily have been necessary in some patients. The maintenance of plasma-perhexiline concentrations between 0.15 and 0.60 micrograms/mL has been recommended.

Perhexiline occasionally produces severe adverse effects including peripheral neuropathy affecting all four limbs with associated papilloedema, severe and occasionally fatal hepatic toxicity, and metabolic abnormalities with marked weight loss, hypertriglyceridaemia, and profound hypoglycaemia. It is contra-indicated in patients with hepatic or renal impairment. Perhexiline should be used with caution in diabetic patients. Hepatic metabolism of perhexiline is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore caution is advised if perhexiline is used with other drugs that inhibit or are metabolised by this enzyme, and perhexiline toxicity has been reported with SSRIs such as fluoxetine or paroxetine.

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

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Pexsig; ***NZ:*** Pexsig.

Perindopril *(BAN, USAN, rINN)*

McN-A-2833; Perindopriili; Périndopril; Perindoprilum; S-9490. (2*S*,3a*S*,7a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonylbutyl]-L-alanyl}perhydroindole-2-carboxylic acid.

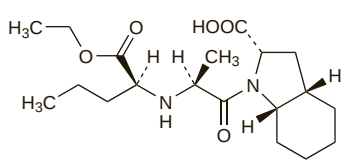
Периндоприл

$C_{19}H_{32}N_2O_5$ = 368.5.

CAS — 82834-16-0.

ATC — C09AA04.

ATC Vet — QC09AA04.



Perindopril Arginine *(BANM, rINNM)*

Perindopril arginina; Périndopril Arginine; Perindoprilum Argininum.

Периндоприл Аргинин

CAS — 612548-45-5.

ATC — C09AA04.

ATC Vet — QC09AA04.

Perindopril Erbumine *(BANM, USAN, rINNM)*

tert-Butilamino perindoprilis; Butylamini Perindoprilum; *Tert*-Butylamini Perindoprilum; Butylamin-perindopril; Erbumina de perindopril; McN-A-2833-109; Perindopriili-*tert*-butyyliamiini; Perindopril *tert*-Butylamine; Périndopril, Erbumine de; Perindopril Terbutalamin; Périndopril tert-butylamine; Perindopril-*tert*-butylamin; Perindopril-erbumin; Perindoprili Erbuminum; Perindoprilum Erbuminum; Peryndopryl z tert-butyloaminą; S-9490-3; tert-Butylamini perindoprilum.

Периндоприла Эрбумин

$C_{19}H_{32}N_2O_5,C_4H_{11}N$ = 441.6.

CAS — 107133-36-8.

ATC — C09AA04.

ATC Vet — QC09AA04.

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

Ph. Eur. 6.2 (Perindopril *tert*-Butylamine; Perindopril Erbumine BP 2008). A white or almost white, slightly hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water and in alcohol; soluble or sparingly soluble in dichloromethane. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

◊ In a postmarketing surveillance study[1] of 47 351 patients receiving perindopril for hypertension, no unexpected adverse effects were reported and serious reactions were rare; 1587 (6.3%) women and 782 (3.5%) men withdrew from therapy due to adverse effects.

Although a study[2] of perindopril use in patients with stable chronic heart failure reported no significant first-dose hypotension, there has been a case report[3] of ischaemic stroke, possibly associated with hypotension, after a single dose of perindopril in a patient with post-infarction heart failure. Standard precautions as for other ACE inhibitors (p.1195) should be followed when starting perindopril therapy.

1. Speirs C, *et al.* Perindopril postmarketing surveillance: a 12 month study in 47 351 hypertensive patients. *Br J Clin Pharmacol* 1998; **46:** 63–70.
2. MacFadyen RJ, *et al.* Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study. *Br Heart J* 1991; **66:** 206–11.
3. Bagger JP. Adverse event with first-dose perindopril in congestive heart failure. *Lancet* 1997; **349:** 1671–2.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Perindopril acts as a prodrug of the diacid perindoprilat, its active form. After oral doses perindopril is rapidly absorbed with a bioavailability of about 65 to 75%. It is extensively metabolised, mainly in the liver, to perindoprilat and inactive metabolites including glucuronides. The presence of food is reported to reduce the conversion of perindopril to perindoprilat. Peak plasma concentrations of perindoprilat are achieved 3 to 4 hours after an oral dose of perindopril. Perindoprilat is about 10 to 20% bound to plasma proteins. Perindopril is excreted predominantly in the urine, as unchanged drug, as perindoprilat, and as other metabolites. The elimination of perindoprilat is biphasic with a distribution half-life of about 5 hours and an elimination half-life of 25 to 30 hours or longer, the latter half-life probably representing strong binding to angiotensin-converting enzyme. The excretion of perindoprilat is decreased in renal impairment. Both perindopril and perindoprilat are removed by dialysis.

◊ References.

1. Lecocq B, *et al.* Influence of food on the pharmacokinetics of perindopril and the time course of angiotensin-converting enzyme inhibition in serum. *Clin Pharmacol Ther* 1990; **47:** 397–402.
2. Verpooten GA, *et al.* Single dose pharmacokinetics of perindopril and its metabolites in hypertensive patients with various degrees of renal insufficiency. *Br J Clin Pharmacol* 1991; **32:** 187–92.
3. Sennesael J, *et al.* The pharmacokinetics of perindopril and its effects on serum angiotensin converting enzyme activity in hypertensive patients with chronic renal failure. *Br J Clin Pharmacol* 1992; **33:** 93–9.
4. Thiollet M, *et al.* The pharmacokinetics of perindopril in patients with liver cirrhosis. *Br J Clin Pharmacol* 1992; **33:** 326–8.
5. Guérin A, *et al.* The effect of haemodialysis on the pharmacokinetics of perindoprilat after long-term perindopril. *Eur J Clin Pharmacol* 1993; **44:** 183–7.

Uses and Administration

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

(p.1165). It is also used to reduce the risk of cardiovascular events in patients with stable ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164).

Perindopril is converted in the body into its active metabolite perindoprilat. ACE inhibition is reported to occur within 1 hour of a dose, to be at a maximum at about 4 to 8 hours, and to be maintained for 24 hours. Perindopril is given orally as the erbumine salt and should be taken before food. In some countries perindopril is also available as the arginine salt; 5 mg of perindopril arginine is equivalent to about 4 mg of perindopril erbumine.

In the treatment of **hypertension** perindopril is given in an initial dose of 4 mg of the erbumine or 5 mg of the arginine salt 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. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and in such patients the initial dose may be halved to 2 or 2.5 mg respectively once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before perindopril is started and resumed later if required; if this is not possible, the initial dose may be halved similarly. The same lower initial dose may also be used in the elderly. The dose of perindopril may be increased according to response to a maximum of 8 mg of the erbumine or 10 mg of the arginine salt daily. In the USA a maximum dose of 16 mg of perindopril erbumine daily is allowed in uncomplicated hypertension.

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 be initiated with a low dose under close medical supervision. Perindopril is given in an initial dose of 2 mg of the erbumine or 2.5 mg of the arginine salt in the morning. The usual maintenance dose is 4 mg or 5 mg respectively daily.

In the management of patients with **ischaemic heart disease** perindopril is given in an initial dose of 4 mg (erbumine) or 5 mg (arginine) once daily for 2 weeks, then titrated up to a maintenance dose of 8 or 10 mg respectively once daily if tolerated. Elderly patients should be started on 2 or 2.5 mg once daily for the first week.

Dosage should be reduced in patients with impaired renal function (see below).

◊ References.

1. Todd PA, Fitton A. Perindopril: a review of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1991; **42:** 90–114.
2. Doyle AE, ed. Angiotensin-converting enzyme (ACE) inhibition: benefits beyond blood pressure control. *Am J Med* 1992; **92** (suppl 4B): 1S–107S.
3. Hurst M, Jarvis B. Perindopril: an updated review of its use in hypertension. *Drugs* 2001; **61** 867–96.
4. Simpson D, *et al*. Perindopril: in congestive heart failure. *Drugs* 2002; **62:** 1367–77.
5. Curran MP, *et al*. Perindopril: a review of its use in patients with or at risk of developing coronary artery disease. *Drugs* 2006; **66:** 235–55.
6. Telejko E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. *Curr Med Res Opin* 2007; **23:** 953–60.

Administration in renal impairment. The dose of perindopril should be reduced in patients with renal impairment. UK licensed product information recommends the following doses:

- creatinine clearance (CC) between 30 and 60 mL/minute: 2 mg of the erbumine or 2.5 mg of the arginine salt daily
- CC between 15 and 30 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on alternate days
- CC less than 15 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on dialysis days.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Coverene; ***Austral.:*** Coversyl; Perindo; ***Austria:*** Coversum; ***Belg.:*** Coversyl; ***Braz.:*** Coversyl; ***Canad.:*** Coversyl; ***Chile:*** Coversyl; ***Cz.:*** Apo-Perindo; Cordesyl; Covedaspen; Covemarin; Covemedal; Covepet; Coverdosyn; Coverdyne; Coverex; Coversidin; Coversyspes; Covethanar; Prenessa; Prestarium; Prestarium Neo; Prexanil; Pricoron; ***Denm.:*** Coversyl; ***Fin.:*** Coversyl; ***Fr.:*** Coversyl; ***Ger.:*** Coversum; ***Gr.:*** Coversyl; ***Hong Kong:*** Acertil; ***Hung.:*** Armix; Coverex; Perindan; Prenessa; ***India:*** Coversyl; Perigard; ***Indon.:*** Prexum; ***Irl.:*** Coversyl; ***Ital.:*** Coversyl; Procaptan; ***Jpn:*** Coversyl; ***Malaysia:*** Covapril; Coversyl; Perinace; ***Mex.:*** Coversyl; ***Neth.:*** Coverex; Coversyl; ***NZ:*** Coversyl; ***Philipp.:*** Coversyl; ***Pol.:*** Coverex; Irpax; Prenessa; Prestarium; ***Port.:*** Coversyl; Ostion; Prexum; ***Rus.:*** Prestarium (Престариум); ***S.Afr.:*** Coversyl; Prexum; ***Singapore:*** Coversyl; ***Spain:*** Coversyl; ***Switz.:*** Coversum; ***Thai.:*** Coversyl; ***Turk.:*** Coversyl; ***UK:*** Coversyl; ***USA:*** Aceon; ***Venez.:*** Coversyl.

Multi-ingredient: ***Arg.:*** Bipreterax; Preterax; ***Austral.:*** Coversyl Plus; ***Austria:*** Predonium; Preterax; ***Belg.:*** Bi Preterax; Coversyl Plus; Preterax; ***Braz.:*** Coversyl Plus; ***Canad.:*** Coversyl Plus; Preterax; ***Cz.:*** Noliprel; Prenewel; Prestarium Combi; Prestarium Neo Combi; ***Denm.:*** Coversyl Comp; ***Fin.:*** Coversyl Comp; ***Fr.:*** Bipreterax; Preterax; ***Ger.:*** Coversum Combi; Preterax; ***Gr.:*** Preterax; ***Hong Kong:*** Predonium; ***Hung.:*** Armix Komb; Armix Prekomb; Co-Prenessa; Coverex Komb; Coverex Prekomb; Noliprel†; Noriplex†; ***India:*** Coversyl Plus; Perigard D; Perigard DF; ***Irl.:*** Bipreterax; Coversyl Plus; Preterax; ***Ital.:*** Prelectal; Preterax; ***Malaysia:*** Coversyl Plus; ***Mex.:*** Preterax; ***Neth.:*** Coversyl Plus; Predonium; Preterax; ***NZ:*** Coversyl Plus; Predonium; ***Philipp.:*** Bi-Preterax; Preterax; ***Pol.:*** Noliprel; Prestarium Plus; ***Port.:*** Bi Predonium; Bi Preterax; Predonium; Preterax; ***Rus.:*** Noliprel (Нолипрел); ***S.Afr.:*** Bipreterax; Coversyl Plus; Preterax; Prexum Plus; ***Singapore:*** Coversyl Plus; Preterax; ***Spain:*** Bipredonium†; Bipreterax; Preterax; ***Switz.:*** Coversum Combi; Preterax; ***Turk.:*** Coversyl Plus; Preterax; ***UK:*** Coversyl Plus; ***Venez.:*** Bipreterax; Preterax.

Phenindione *(BAN, rINN)*

Fenindion; Fenindiona; Fenindione; Fenindioni; Phénindione; Phenindionum; Phenylindanedione; Phenylinium. 2-Phenylindan-1,3-dione.

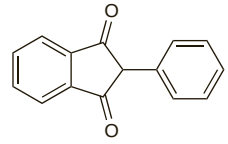
Фениндион

$C_{15}H_{10}O_2$ = 222.2.

CAS — 83-12-5.

ATC — B01AA02.

ATC Vet — QB01AA02.



Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Phenindione). Soft, odourless or almost odourless, white or creamy-white crystals. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Solutions are yellow to red.

Adverse Effects and Treatment

As for Warfarin Sodium, p.1425. However, phenindione and the other indanediones are generally more toxic than warfarin with hypersensitivity reactions involving many organs and sometimes resulting in death. Some of the reactions include skin rashes and exfoliative dermatitis, pyrexia, diarrhoea, vomiting, sore throat, liver and kidney damage, myocarditis, agranulocytosis, leucopenia, eosinophilia, and a leukaemoid syndrome.

Phenindione may discolour the urine pink or orange and this is independent of any haematuria. Taste disturbances have been reported.

Effects on the gastrointestinal tract. There have been cases of paralytic ileus, one fatal, associated with phenindione.[1,2]

1. Menon IS. Phenindione and paralytic ileus. *Lancet* 1966; **i:** 1421–2.
2. Nash AG. Phenindione and paralytic ileus. *Lancet* 1966; **ii:** 51–2.

Precautions

As for Warfarin Sodium, p.1426.

Phenindione is not recommended in pregnancy.

Breast feeding. Phenindione is distributed into breast milk, with reported concentrations[1] of 1 to 5 micrograms/mL after a single dose of 50 or 75 mg. A woman receiving phenindione 50 mg each morning and 50 and 25 mg on alternate nights breast-fed her infant son,[2] who required a herniotomy at 5 weeks. After surgery he had an enormous scrotal haematoma and oozing from the wound, and was found to have extended prothrombin and partial thromboplastin times. The American Academy of Pediatrics therefore considers[3] that phenindione should be given with caution to breast-feeding mothers.

1. Goguel M, *et al*. Thérapeutique anticoagulante et allaitement: etude du passage de la phényl-2-dioxo, 1,3 indane dans le lait maternel. *Rev Fr Gynecol Obstet* 1970; **65:** 409–12.
2. Eckstein HB, Jack B. Breast-feeding and anticoagulant therapy. *Lancet* 1970; **i:** 672–3.
3. 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 06/07/04)

Interactions

The interactions associated with oral anticoagulants are described in detail under warfarin (p.1427). Specific references to interactions involving phenindione can be found there under the headings for the following drug groups: analgesics; antibacterials; antifungals; antiplatelets; anxiolytic sedatives; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenindione is absorbed from the gastrointestinal tract. It crosses the placenta and is distributed into breast milk. Metabolites of phenindione excreted in the urine are responsible for any discoloration that may occur.

Uses and Administration

Phenindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187), but because of its higher incidence of severe adverse effects it is now rarely employed.

The usual initial dose of phenindione is 200 mg on the first day, 100 mg on the second day, and then maintenance doses of 50 to 150 mg daily according to coagulation tests.

Preparations

BP 2008: Phenindione Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Dindevan; ***Fr.:*** Pindione†; ***India:*** Dindevan.

Phenoxybenzamine Hydrochloride

(BANM, rINNM)

Fenoksybenzaminy chlorowodorek; Hidrocloruro de fenoxibenzamina; Phénoxybenzamine, Chlorhydrate de; Phenoxybenzamini Hydrochloridum; SKF-688A. Benzyl(2-chloroethyl)(1-methyl-2-phenoxyethyl)amine hydrochloride.

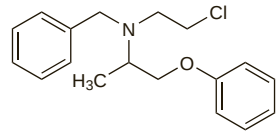
Феноксибензамина Гидрохлорид

$C_{18}H_{22}ClNO,HCl$ = 340.3.

CAS — 59-96-1 (phenoxybenzamine); 63-92-3 (phenoxybenzamine hydrochloride).

ATC — C04AX02.

ATC Vet — QC04AX02.



(phenoxybenzamine)

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2008 (Phenoxybenzamine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform.

Adverse Effects and Treatment

The adverse effects of phenoxybenzamine are mainly due to its alpha-adrenoceptor blocking activity. They include orthostatic hypotension and dizziness, reflex tachycardia, nasal congestion, and miosis. Inhibition of ejaculation may occur. These effects may be minimised by using a low initial dose, and may diminish with continued use, but the hypotensive effect can be exaggerated by exercise, heat, a large meal, or alcohol ingestion. Other side-effects include dry mouth, decreased sweating, drowsiness, fatigue, and confusion. Gastrointestinal effects are usually slight. When phenoxybenzamine is given intravenously, idiosyncratic profound hypotension can occur within a few minutes of starting the infusion. Convulsions have been reported after rapid intravenous infusion of phenoxybenzamine.

Severe hypotension may occur in overdose and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement. Sympathomimetics are considered to be of little value, and adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia. Sources differ as to the value of noradrenaline in overcoming alpha-receptor blockade.

Phenoxybenzamine has been shown to be mutagenic in *in vitro* tests and carcinogenic in *rodents*.

Precautions

Phenoxybenzamine should be given with care to patients with heart failure, ischaemic heart disease, cerebrovascular disease, or renal impairment, and should be avoided if a fall in blood pressure would be dangerous. Phenoxybenzamine may aggravate the symptoms of respiratory infections.