was no evidence that Egyptian patients metabolised the drug differently to produce a pyrogenic metabolite, and the effect had not been seen in other areas where a similar high-dose regimen was used.[1]

1. Foster R. A review of clinical experience with oxamniquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 55–9.

Effects on the nervous system. In 37 patients with *Schistosoma mansoni* infection treated successfully with oxamniquine,[1] dizziness and drowsiness were most common, but the most significant adverse effect was the development of EEG abnormalities in 6 of 34 patients whose pre-treatment EEG was normal. Of the 3 patients with pre-existing EEG abnormalities, 1 suffered a tonic-clonic seizure during therapy as previously reported,[2] 1 did not suffer seizures, and the third received phenytoin prophylaxis during oxamniquine therapy. It was considered prudent to give antiepileptics before starting oxamniquine in patients with a history of seizure disorder. After completion of this study, a patient with no history of seizures suffered a tonic-clonic seizure 2 hours after each of the second and third doses of oxamniquine.

The main neuropsychiatric adverse effects seen in 180 Brazilian patients with *Schistosoma mansoni* infection treated with single oral doses of oxamniquine were: drowsiness (50.6%), dizziness (41.1%), headache (16.1%), temporary amnesia (2.2%), behavioural disturbances (1.7%), chills (1.1%), and seizures (1.1%).[3] An EEG was performed before and after treatment in 20 patients; there were alterations in 3 but they were not associated with neuropsychiatric changes.

1. Krajden S, *et al*. Safety and toxicity of oxamniquine in the treatment of Schistosoma mansoni infections, with particular reference to electroencephalographic abnormalities. *Am J Trop Med Hyg* 1983; **32:** 1344–6.
2. Keystone JS. Seizures and electroencephalograph changes associated with oxamniquine therapy. *Am J Trop Med Hyg* 1978; **27:** 360–2.
3. de Carvalho SA, *et al*. Neurotoxicidade do oxamniquine no tratamento da infeção humana pelo Schistosoma mansoni. *Rev Inst Med Trop Sao Paulo* 1985; **27:** 132–42.

Precautions

Oxamniquine should be used with caution in patients with epilepsy or a history of convulsive disorders. Patients should be warned that oxamniquine can cause dizziness or drowsiness and if affected they should not drive or operate machinery.

Pharmacokinetics

Oxamniquine is readily absorbed after oral doses. Peak plasma concentrations are achieved 1 to 3 hours after a dose and the plasma half-life is 1 to 2.5 hours.

It is extensively metabolised to inactive metabolites, principally the 6-carboxy derivative, which are excreted in the urine. About 70% of a dose of oxamniquine is excreted as the 6-carboxy metabolite within 12 hours of a dose; traces of the 2-carboxy metabolite have also been detected in the urine.

Uses and Administration

Oxamniquine is an anthelmintic used in the treatment of schistosomiasis caused by *Schistosoma mansoni*, but not by other *Schistosoma* spp. It causes worms to shift from the mesenteric veins to the liver where the male worms are retained; the female worms return to the mesentery, but can no longer release eggs. Resistance may occur.

Oxamniquine is given orally, preferably after food. Dosage depends on the geographical origin of the infection and total doses range from 15 mg/kg as a single dose to 60 mg/kg given over 2 to 3 days. A single dose should not exceed 20 mg/kg.

Schistosomiasis. Oxamniquine is an alternative to praziquantel for the treatment of schistosomiasis (p.138) due to *Schistosoma mansoni*, although resistance has occurred, particularly in South America,[1] and it is somewhat less effective than praziquantel.[2]

The dose ranges between a single dose of 15 mg/kg and 60 mg/kg given over 2 or 3 days.[1,3] Doses in the low range have been used effectively in South America, the Caribbean, and West Africa while patients in Egypt, South Africa, and Zimbabwe require doses at the top end of the range; intermediate doses may be effective in other parts of Africa.[3]

After the appropriate therapeutic dose of oxamniquine, cure rates of at least 60%, and often more than 90%, can be expected. Egg excretion in those not cured will be reduced by over 80%, and usually by over 90%, one year after treatment.[3]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Ferrari ML, *et al*. Efficacy of oxamniquine and praziquantel in the treatment of Schistosoma mansoni infection: a controlled trial. *Bull WHO* 2003; **81:** 190–6.
3. WHO. The control of schistosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 728* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_728.pdf (accessed 16/07/08)

Preparations

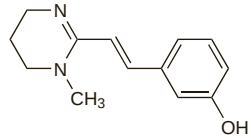
Proprietary Preparations (details are given in Part 3)
Braz.: Mansil; ***Gr.:*** Vansil†.

Oxantel Embonate *(BANM, rINNM)*

CP-14445-16; Embonato de oxantel; Oxantel, Embonate d'; Oxantel Pamoate *(USAN)*; Oxanteli Embonas. (*E*)-3-[2-(1,4,5,6-Tetrahydro-1-methylpyrimidin-2-yl)vinyl]phenol 4,4′-methylenebis(3-hydroxy-2-naphthoate).

Оксантела Эмбонат

$C_{13}H_{16}N_2O,C_{23}H_{16}O_6$ = 604.6.
CAS — 36531-26-7 (oxantel); 68813-55-8 (oxantel embonate); 42408-84-4 (oxantel embonate).
ATC — P02CC02.



(oxantel)

Profile

Oxantel is an analogue of pyrantel that has been used as the embonate in the treatment of trichuriasis. It is used with pyrantel for various intestinal nematode infections.

Preparations

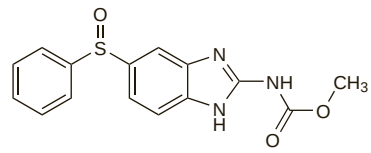
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Indon.:*** Quantrel; ***Philipp.:*** Quantrel; ***Venez.:*** Dualid; Quantrel.

Oxfendazole *(BAN, USAN, rINN)*

Oksfendatsoli; Oxfendazol; Oxfendazolum; RS-8858. Methyl 5-phenylsulphinyl-1*H*-benzimidazol-2-ylcarbamate.

Оксфендазол

$C_{15}H_{13}N_3O_3S$ = 315.3.
CAS — 53716-50-0.
ATC Vet — QP52AC02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.
Ph. Eur. 6.2 (Oxfendazole for Veterinary Use; Oxfendazole BP(Vet) 2008). A white or almost white powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.
USP 31 (Oxfendazole). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

Profile

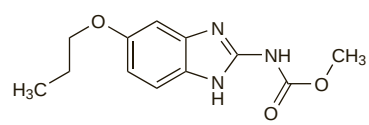
Oxfendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p.148). It is used in veterinary medicine.

Oxibendazole *(BAN, USAN, rINN)*

Oxibendazol; Oxibendazolum; SKF-30310. Methyl 5-propoxy-1*H*-benzimidazol-2-ylcarbamate.

Оксибендазол

$C_{12}H_{15}N_3O_3$ = 249.3.
CAS — 20559-55-1.
ATC Vet — QP52AC07.



Profile

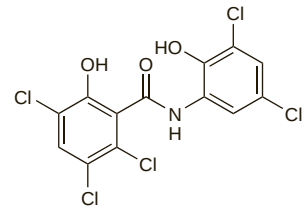
Oxibendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p.148). It is used in veterinary medicine.

Oxyclozanide *(BAN, rINN)*

ICI-46683; Oxiclozanida; Oxyclozanidum. 3,3′,5,5′,6-Pentachloro-2′-hydroxysalicylanilide.

Оксиклозанид

$C_{13}H_6Cl_5NO_3$ = 401.5.
CAS — 2277-92-1.
ATC Vet — QP52AG06.



Pharmacopoeias. In *BP(Vet)*.
BP(Vet) 2008 (Oxyclozanide). A pale cream or cream-coloured powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone; slightly soluble in chloroform.

Profile

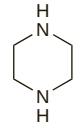
Oxyclozanide is an anthelmintic used in veterinary medicine for the control of fascioliasis in cattle and sheep.

Piperazine

Piperatsiini; Piperazin; Piperazina; Piperazinum.

Пиперазин

$C_4H_{10}N_2$ = 86.14.
CAS — 110-85-0.
ATC — P02CB01.
ATC Vet — QP52AH01.



Pharmacopoeias. In *US*.
USP 31 (Piperazine). White to off-white lumps or flakes having an ammoniacal odour. Soluble in water and in alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Piperazine Adipate

Piperatsiiniadipaatti; Piperaz. Adip.; Piperazina, adipato de; Piperazinadipat; Piperazin-adipát; Pipérazine, adipate de; Piperazini adipas; Piperazino adipatas; Piperazinum Adipicum.

Пиперазина Адипат

$C_4H_{10}N_2,C_6H_{10}O_4$ = 232.3.
CAS — 142-88-1.
ATC — P02CB01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet*.
Ph. Eur. 6.2 (Piperazine Adipate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol.

Piperazine Citrate

Hydrous Tripiperazine Dicitrate; Piperatsiinisitraatti; Piperazina, citrato de; Piperazincitrat; Piperazin-citrát; Piperazin-citrát hydrát; Pipérazine, citrate de; Piperazini citras; Piperazini Citras Hydricus; Piperazino citratas.

Пиперазина Цитрат

$(C_4H_{10}N_2)_3,2C_6H_8O_7,xH_2O$ = 642.7 (anhydrous substance).
CAS — 144-29-6 (anhydrous piperazine citrate); 41372-10-5 (piperazine citrate hydrate).
ATC — P02CB01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet*.
Ph. Eur. 6.2 (Piperazine Citrate). A white or almost white granular powder. It contains a variable amount of water. Freely soluble in water; practically insoluble in alcohol.
USP 31 (Piperazine Citrate). A white, crystalline powder having not more than a slight odour. Soluble in water; insoluble in alcohol and in ether. pH of a 10% solution in water is about 5.

Stability. A decrease in the content of piperazine [as citrate] in syrups on storage was attributed to interaction with fructose and glucose formed by hydrolysis of sucrose.[1] A syrup prepared with sorbitol lost no potency when stored at 25° for 14 months.

1. Nielsen A, Reimer P. The stability of piperazine in syrup. *Arch Pharm Chemi (Sci)* 1975; **3:** 73–8.

Piperazine Hydrate

Piperatsiinihydraatti; Piperazin Heksahidrat; Piperazin hexahydrát; Piperazina hexahidrato; Piperazinas hidratas; Pipérazine, hydrate de; Piperazin-hidrát; Piperazinhydrat; Piperazini Hydras; Piperazinium Hexahydricum; Piperazinum hydricum; Piperazyna uwodniona. Piperazine hexahydrate.

Пиперазина Гидрат

$C_4H_{10}N_2,6H_2O$ = 194.2.

CAS — 142-63-2.

ATC — P02CB01.

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

Ph. Eur. 6.2 (Piperazine Hydrate). Colourless deliquescent crystals. M.p. about 43°. Freely soluble in water and in alcohol. A 5% solution in water has a pH of 10.5 to 12.0. Store in airtight containers. Protect from light.

Piperazine Phosphate

Piperazina, fosfato de; Piperazini Phosphas.

Пиперазина Фосфат

$C_4H_{10}N_2,H_3PO_4,H_2O$ = 202.1.

CAS — 14538-56-8 (anhydrous piperazine phosphate); 18534-18-4 (piperazine phosphate monohydrate).

ATC — P02CB01.

Pharmacopoeias. In *Br., Chin., Jpn,* and *Viet.*

BP 2008 (Piperazine Phosphate). A white odourless or almost odourless crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.5.

Adverse Effects

Serious adverse effects are rare with piperazine and generally indicate overdosage or impaired excretion. Nausea, vomiting, diarrhoea, abdominal pain, headache, skin rashes, and urticaria occasionally occur. Severe neurotoxicity and EEG abnormalities have been reported with symptoms including somnolence, dizziness, nystagmus, muscular incoordination and weakness, ataxia, paraesthesia, myoclonic contractions, choreiform movements, tremor, convulsions, and loss of reflexes.

Transient visual disturbances such as blurred vision have occurred occasionally and there were reports of cataract formation after treatment with piperazine although they do not appear to have been substantiated.

Hypersensitivity reactions such as bronchospasm, Stevens-Johnson syndrome, and angioedema have occurred in some individuals.

◊ Piperazine has been taken off the market in some European countries because of general concern about its safety.[1] A study carried out in Sweden on 2 healthy subjects had indicated that mononitrosation of piperazine can occur in the stomach to produce the potential carcinogen *N*-mononitrosopiperazine; the more potent *N,N*-dinitrosopiperazine was not found.[2] However, the disease risk to man from such *N*-nitroso compounds has been questioned[3] and certainly reports of tumours associated with the use of piperazine have not been traced. Also, in the UK the CSM concluded that the incidence of serious adverse effects associated with piperazine was low and that, with appropriate pack warnings, piperazine products could remain as medicines available to the public through pharmacies.[1]

1. Anonymous. Data sheet changes for piperazine in pregnancy. *Pharm J* 1988; **240:** 367.
2. Bellander BTD, *et al.* Nitrosation of piperazine in the stomach. *Lancet* 1981; **ii:** 372.
3. Tannenbaum SR. N-nitroso compounds: a perspective on human exposure. *Lancet* 1983; **i:** 629–32.

Abuse. Derivatives of piperazine have been developed and abused as 'designer drugs'—see Benzylpiperazine (p.2152).

Effects on the blood. A 4-year-old African boy with G6PD deficiency developed haemolytic anaemia; no cause for the haemolysis was found except that 2 days previously he had taken *Pripsen* (piperazine and senna).[1] Severe thrombocytopenia with epistaxis and haemoptysis, which developed in a 61-year-old man after piperazine self-medication, was probably the result of sensitisation to piperazine 15 years earlier.[2]

1. Buchanan N, *et al.* G-6-PD deficiency and piperazine. *BMJ* 1971; **2:** 110.
2. Cork MJ, *et al.* Pruritus ani, piperazine, and thrombocytopenia. *BMJ* 1990; **301:** 1398.

Effects on the liver. A reaction resembling viral hepatitis occurred on 2 occasions in a 25-year-old woman after use of piperazine; it appeared to be a hypersensitivity reaction.[1]

1. Hamlyn AN, *et al.* Piperazine hepatitis. *Gastroenterology* 1976; **70:** 1144–7.

Hypersensitivity. A patient experienced a serum-sickness-like illness associated with piperazine,[1] which was followed by a delayed hypersensitivity vasculitis.

See also Effects on the Blood and Effects on the Liver, above.

1. Balzan M, Cacciottolo JM. Hypersensitivity vasculitis associated with piperazine therapy. *Br J Dermatol* 1994; **131:** 133–4.

Precautions

Piperazine is contra-indicated in patients with epilepsy or severe renal impairment and should be given with care to patients with neurological disturbances or mild to moderate renal impairment. It should also be avoided or given with extreme caution in patients with hepatic impairment.

Breast feeding. The UK licensed product information for *Pripsen* (piperazine and senna) states that piperazine is distributed into breast milk. Mothers should be advised to take a dose after breast feeding then not to breast feed for 8 hours during which period milk should be expressed and discarded at the regular feeding times.

Pregnancy. It has been reported that piperazine is teratogenic in *rabbits* and that there have been isolated reports of fetal malformations after clinical use, though no causal relationship has been established. Two infants with malformations have been described briefly:[1] one had bilateral hare lip, cleft palate, and anophthalmia; the other had an abnormality of one foot. Both mothers had taken *Pripsen* (piperazine and senna). UK licensed product information for *Pripsen* advises against use in pregnancy, especially during the first trimester, unless immediate treatment with piperazine is essential.

1. Leach FN. Management of threadworm infestation during pregnancy. *Arch Dis Child* 1990; **65:** 399–400.

Interactions

The anthelmintic effects of piperazine and pyrantel may be antagonised when the two compounds are used together. The possibility that piperazine may enhance the adverse effects of phenothiazines such as chlorpromazine is discussed on p.975.

Pharmacokinetics

Piperazine is readily absorbed from the gastrointestinal tract and is excreted in the urine within 24 hours, partly as metabolites. The rate at which different individuals excrete piperazine has been reported to vary widely. It is distributed into breast milk.

Uses and Administration

Piperazine is an anthelmintic effective against the intestinal nematodes *Ascaris lumbricoides* (roundworm) and *Enterobius vermicularis* (pinworm, threadworm), although other anthelmintics are usually preferred (see the discussions on the treatment of ascariasis and enterobiasis on p.134 and p.136). In roundworms piperazine produces a neuromuscular block leading to a flaccid muscle paralysis in susceptible worms, which are then easily dislodged by the movement of the gut and expelled in the faeces.

Piperazine is usually given as the citrate or phosphate, but the adipate may also be used. The dosage of the salts of piperazine is usually expressed in terms of piperazine hydrate; 100 mg of piperazine hydrate is equivalent to about 44.4 mg of piperazine, 120 mg of piperazine adipate, 125 mg of piperazine citrate (110 mg of anhydrous piperazine citrate), and to 104 mg of piperazine phosphate.

For the treatment of ascariasis, a single dose, repeated once after 14 days, has been used. In adults and children over 12 years of age, a dose equivalent to 4.5 g of piperazine hydrate is given orally. Children aged 9 to 12 years may be given the equivalent of 3.75 g, those aged 6 to 8 years the equivalent of 3 g, those aged 4 to 5 years the equivalent of 2.25 g, and those aged 1 to 3 years the equivalent of 1.5 g. Children under 1 year should receive piperazine on medical advice only; a dose equivalent to 120 mg/kg has been suggested.

For enterobiasis, piperazine has been given for 7 days. A second course after a 7-day interval may be required. Adults and children over 12 years of age are given the equivalent of 2.25 g of the hydrate once daily, children aged 7 to 12 years the equivalent of 1.5 g daily, those aged 4 to 6 years the equivalent of 1.125 g daily, and those aged 1 to 3 years the equivalent of 750 mg daily. Children under 1 year should receive piperazine on medical advice only; a dose equivalent to 45 to 75 mg/kg has been suggested.

Piperazine is also used as a preparation with senna in a single dose of 4 g of the phosphate for adults and children over 6 years of age, repeated after 14 days for enterobiasis, or repeated monthly if necessary for up to 3 months to treat and prevent ascariasis.

Preparations

BP 2008: Piperazine Citrate Elixir; Piperazine Phosphate Tablets;
USP 31: Piperazine Citrate Syrup; Piperazine Citrate Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Ascarinase†; Ortovermim†; Vermifran†; Vermilen†; ***Canad.:*** Entacyl†; ***Fr.:*** Vermifuge†; ***Indon.:*** Combicitrine; Piperacyl; Upixon; ***Ital.:*** Citropiperazina; ***Mex.:*** Desparasil†; Helmifar†; Lu-Peracina; Overpon; Piperawitt DS†; Piperazil; Pipergress; Pipermed†; Pirzinol; Verfid; Vermin; ***Port.:*** Lombrimade†; Pipermel; Pipertox; ***S.Afr.:*** Padax; Pipralen; Piprine; SB Tox Worm; ***Spain:*** Mimedran; Vermi; ***Thai.:*** Vermex; ***Turk.:*** Asepar; Askaripar; Helmicide; Helmipar; Oksiaskaril; Siropar; ***UK:*** Pripsen†; ***Venez.:*** Ciperina; Inquiper†; Jetsan†; Oxine†; Piperato; Piperazil; Piperdin; Piperzan; Verpirol.

Multi-ingredient: ***Braz.:*** Vermilen Composto†; ***India:*** Helmazan†; ***Irl.:*** Pripsen†; ***Port.:*** Biureol; ***UK:*** Pripsen.

Pomegranate Bark

Granado; Granati Cortex; Granatrinde; Granatum; Grenadier; Melograno; Pomegranate; Pomegranate Root Bark; Romeira.

Кора Гранатового Дерева

Profile

Pomegranate bark, the dried bark of the stem and root of *Punica granatum* (Punicaceae) containing about 0.4 to 0.9% of alkaloids,, has been used for the expulsion of tapeworms.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Hexaporine.

Praziquantel *(BAN, USAN, rINN)*

EMBAY-8440; Pratsikvanteli; Prazicuantel; Prazikvantel; Prazikvantelis; Praziquantelum. 2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydropyrazino[2,1-*a*]isoquinolin-4-one.

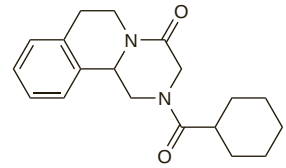
Празиквантел

$C_{19}H_{24}N_2O_2$ = 312.4.

CAS — 55268-74-1.

ATC — P02BA01.

ATC Vet — QP52AA01.



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

Ph. Eur. 6.2 (Praziquantel). White or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Praziquantel). A white or practically white crystalline powder; odourless or with a faint characteristic odour. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Protect from light.

Adverse Effects

Adverse effects with praziquantel may be common but are usually mild and transient. Headache, diarrhoea, dizziness, drowsiness, malaise, abdominal discomfort, nausea, and vomiting have been reported most frequently. Hypersensitivity reactions such as fever, urticaria, pruritic skin rashes, and eosinophilia can occur; they may be due to death of the infecting parasites. Raised liver enzyme values have been reported rarely.

Most patients with neurocysticercosis who are given praziquantel suffer CNS effects, including headache, hyperthermia, seizures, and intracranial hypertension, which are thought to result from an inflammatory re-