Paromomycin is given as the sulfate although doses are expressed in terms of the base. In intestinal amoebiasis, the dose for both adults and children is the equivalent of paromomycin 25 to 35 mg/kg daily in 3 divided oral doses with meals for 5 to 10 days. Similar doses have been tried in cryptosporidiosis.

In taeniasis and other tapeworm infections, a dose of 4 g is given orally as a single dose or in divided doses over the course of one hour.

For hepatic coma, 4 g is given daily in divided oral doses at regular intervals for 5 to 6 days.

Leishmaniasis. Topical treatment with paromomycin 15% plus methylbenzethonium chloride 5 or 12% has produced promising results[1-3] in *cutaneous leishmaniasis* (p.824); paromomycin 12 to 15% with urea 10% was better tolerated.[4] However, benefit has not been seen in all studies.[5,6] Treatment with topical paromomycin plus systemic meglumine antimonate was initially promising in patients with New World cutaneous leishmaniasis;[7] however, a subsequent study[8] found no clear advantage over treatment with meglumine antimonate alone. Good responses to parenteral paromomycin 14 mg/kg daily, with sodium stibogluconate 10 mg/kg daily, in cases of *diffuse cutaneous leishmaniasis* have also been reported.[9]

Paromomycin has also been used intramuscularly, either alone[10] or with sodium stibogluconate,[11] in the treatment of *visceral leishmaniasis* in an area of India with increasing resistance to pentavalent antimony compounds. The authors of one study[10] found paromomycin 16 or 20 mg/kg daily for 21 days to be significantly more effective than sodium stibogluconate 20 mg/kg daily for 30 days and suggested that paromomycin be considered as first-line treatment for visceral leishmaniasis in this region. Oral paromomycin plus intravenous pentamidine was reported to be effective in the treatment of amphotericin-resistant visceral leishmaniasis in an HIV-infected patient.[12]

1. El-On J, *et al.* Topical treatment of Old World cutaneous leishmaniasis caused by Leishmania major: a double-blind control study. *J Am Acad Dermatol* 1992; **27:** 227–31.
2. Krause G, Kroeger A. Topical treatment of American cutaneous leishmaniasis with paromomycin and methylbenzethonium chloride: a clinical study under field conditions in Ecuador. *Trans R Soc Trop Med Hyg* 1994; **88:** 92–4.
3. Arana BA, *et al.* Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. *Am J Trop Med Hyg* 2001; **65:** 466–70.
4. Bryceson ADM, *et al.* Treatment of Old World cutaneous leishmaniasis with aminosidine ointment: results of an open study in London. *Trans R Soc Trop Med Hyg* 1994; **88:** 226–8.
5. Ben Salah A, *et al.* A randomized, placebo-controlled trial in Tunisia treating cutaneous leishmaniasis with paromomycin ointment. *Am J Trop Med Hyg* 1995; **53:** 162–6.
6. Asilian A, *et al.* A randomized, placebo-controlled trial of a two week regimen of aminosidine (paromomycin) ointment for treatment of cutaneous leishmaniasis in Iran. *Am J Trop Med Hyg* 1995; **53:** 648–51.
7. Soto J, *et al.* Successful treatment of New World cutaneous leishmaniasis with a combination of topical paromomycin/methylbenzethonium chloride and injectable meglumine antimonate. *Clin Infect Dis* 1995; **20:** 47–51.
8. Soto J, *et al.* Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimonate as treatment for American cutaneous leishmaniasis: controlled study. *Clin Infect Dis* 1998; **26:** 56–8.
9. Teklemariam S, *et al.* Aminosidine and its combination with sodium stibogluconate in the treatment of diffuse cutaneous leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1994; **88:** 334–9.
10. Jha TK, *et al.* Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. *BMJ* 1998; **316:** 1200–5.
11. Thakur CP, *et al.* A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. *Trans R Soc Trop Med Hyg* 2000; **94:** 429–31.
12. Manfredi R, *et al.* Diffuse cutaneous dissemination of visceral leishmaniasis during human immunodeficiency virus (HIV) infection, despite negligible immunodeficiency: repeated failure of liposomal amphotericin B administration, followed by successful long-term pentamidine and paromomycin administration. *Int J Antimicrob Agents* 2008; **31:** 590–2.

Trichomoniasis. Local application of a paromomycin cream has been tried in a small number of patients with metronidazole-resistant vaginal trichomoniasis (p.827) with moderate success.[1]

1. Nyirjesy P, *et al.* Difficult-to-treat trichomoniasis: results with paromomycin cream. *Clin Infect Dis* 1998; **26:** 986–8.

Preparations

USP 31: Paromomycin Sulfate Capsules; Paromomycin Sulfate Syrup.

Proprietary Preparations (details are given in Part 3)

Austria: Humatin; ***Belg.:*** Gabbroral; ***Canad.:*** Humatin; ***Ger.:*** Humatin; ***Indon.:*** Gabbryl; ***Ital.:*** Gabbroral; Humatin; Kaman; ***Spain:*** Humatin; ***Switz.:*** Humatin; ***USA:*** Humatin.

Multi-ingredient: ***Israel:*** Leshcutan.

Pentamidine Isetionate *(BANM, rINNM)*

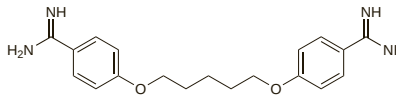
Isetionato de pentamidina; M&B-800; Pentamidiinidi-isetionaatti; Pentamidin Izetiyonat; Pentamidindiisetionat; Pentamidin-diisetionát; Pentamidin-diizetionát; Pentamidine Diisetionate; Pentamidine, diisétionate de; Pentamidine Isethionate *(USAN)*; Pentamidine, Isétionate de; Pentamidini diisetionas; Pentamidini Isethionas; Pentamidini Isetionas; Pentamidino diizetionatas; Pentamidyny diizetionian. 4,4′-(Pentamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulphonate).

Пентамидина Изетионат

$C_{19}H_{24}N_4O_2.2C_2H_6O_4S$ = 592.7.

CAS — 100-33-4 (pentamidine); 140-64-7 (pentamidine isetionate).

ATC — P01CX01.



(pentamidine)

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

Ph. Eur. 6.2 (Pentamidine Diisetionate; Pentamidine Isetionate BP 2008). A white or almost white powder or colourless crystals; it is hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers.

Incompatibility. Immediate precipitation occurred when a solution of pentamidine isetionate 3 mg/mL in glucose 5% was mixed with each of 5 cephalosporin and 1 cephamycin injections.[1]

Pentamidine isetionate is reported to be incompatible with foscarnet.

1. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.

Pentamidine Mesilate *(BANM, rINNM)*

Mesilato de pentamidina; Pentamidine Dimethylsulphonate; Pentamidine, Mésilate de; Pentamidine Mesylate; Pentamidine Methanesulphonate; Pentamidini Mesilas; RP-2512. Pentamidine dimethanesulphonate.

Пентамидина Мезилат

$C_{19}H_{24}N_4O_2.2CH_3SO_3H$ = 532.6.

CAS — 6823-79-6.

Pharmacopoeias. In *Int.*

Adverse Effects

Pentamidine is a toxic drug and adverse effects are frequent and sometimes severe when given parenterally; fatalities have been reported. Renal impairment is common, usually manifesting as mild and reversible raised blood urea nitrogen and serum creatinine concentrations, but acute renal failure can occur. Raised liver enzyme values and haematological disturbances such as leucopenia, anaemia, and occasionally thrombocytopenia, may develop. Hypoglycaemia, sometimes followed by hyperglycaemia and type 1 diabetes mellitus, is well documented; there have been occasional reports of acute pancreatitis.

The rapid intravenous injection of pentamidine has resulted in sudden hypotension and immediate reactions such as dizziness, headache, vomiting, breathlessness, tachycardia, and fainting. Hypotension may also occur when pentamidine is given intramuscularly or by slow intravenous infusion. Intramuscular pentamidine often causes pain, swelling, sterile abscess formation, and tissue necrosis at the site of injection. Similar damage can follow extravasation during intravenous dosage.

Other adverse effects reported include hypocalcaemia, hyperkalaemia, skin rashes, the Stevens-Johnson syndrome, fever, flushing, gastrointestinal effects such as nausea, vomiting, and taste disturbances, confusion, hallucinations, and cardiac arrhythmias.

Pentamidine is not as toxic when given by inhalation for the prophylaxis of pneumocystis pneumonia. The commonest adverse effects with this route are cough and bronchoconstriction and may be controlled by a bronchodilator. Inhalation may leave a bitter taste. Pneumothorax has been reported, but may be associated with the disease. There have been rare reports of adverse effects such as those seen when pentamidine is given by injection.

Incidence of adverse effects. Adverse effects were seen in 46.8% of 404 patients given pentamidine parenterally for the treatment of pneumocystis pneumonia, according to an analysis from the CDC in the USA.[1] The reactions included impaired renal function (23.5% of patients), abnormal liver function (9.6%), hypoglycaemia (6.2%), haematological disturbances (4.2%), skin rashes (1.5%), and hypocalcaemia (1.2%). Local reactions at injection sites such as pain and abscess occurred in 18.3% and immediate adverse effects such as hypotension in 9.6%.

Retrospective studies[2-4] suggest that adverse reactions occur more commonly in patients with AIDS.

An evaluation of pentamidine in the treatment of 82 patients with visceral leishmaniasis further illustrates its toxicity.[5] Cardiotoxicity (tachycardia, hypotension, and ECG changes of non-specific myocarditis), occurred in about 23% of patients. No hypoglycaemic reaction was noted, but 4 patients developed diabetes mellitus and 3 of them were found to be insulin-dependent. Other adverse reactions included gastrointestinal effects (anorexia, nausea, vomiting, abdominal pain, or diarrhoea) in about 78%, CNS effects (headache associated with flushing, delirium, or sensory disturbances resembling pins and needles) in about 24%, mild reversible albuminuria in about 7%, and allergic manifestations (generalised urticaria, itching, and conjunctival congestion) in about 5%. One patient had severe anaphylaxis.

1. Walzer PD, *et al.* Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; **80:** 83–93.
2. Lachaal M, Venuto RC. Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. *Am J Med* 1989; **87:** 260–3.
3. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; **25:** 1171–4.
4. O'Brien JG, *et al.* A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; **24:** 854–9.
5. Jha TK. Evaluation of diamidine compound (pentamidine isethionate) in the treatment of resistant cases of kala-azar occurring in North Bihar, India. *Trans R Soc Trop Med Hyg* 1983; **77:** 167–70.

Effects on the blood. Haemolytic anaemia has been reported in a 55-year-old man with AIDS being treated with intravenous pentamidine for pneumocystis pneumonia. Symptoms developed after a cumulative dose of 3740 mg of pentamidine had been given and resolved several days after stopping the pentamidine.[1]

1. Taguchi H, *et al.* Pentamidine-induced hemolytic anemia in an AIDS patient. *Ann Pharmacother* 1999; **33:** 503.

Effects on carbohydrate metabolism. As reported under Incidence of Adverse Effects, above, pentamidine can have a range of effects on carbohydrate metabolism. Four patients receiving pentamidine for pneumocystis pneumonia developed severe fasting hypoglycaemia followed later by hyperglycaemia and type 1 diabetes mellitus.[1] It has been suggested that pentamidine has a toxic effect on the β-cells of the pancreatic islets and can induce an early cytolytic release of insulin and hypoglycaemia, followed by β-cell destruction, insulin deficiency, and diabetes mellitus.[1,2] AIDS patients appear to be highly susceptible and have a higher incidence of hypoglycaemia due to pentamidine.[3] The action on the pancreas has led to fatal acute *pancreatitis*;[4-6] fatal hypoglycaemia has also been reported.[7] These reports[1-5,7] involved pentamidine given by injection; pancreatitis[8,9] and diabetes mellitus[10,11] have also been reported in patients given pentamidine by aerosol inhalation.

1. Bouchard P, *et al.* Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes* 1982; **31:** 40–5.
2. Osei K, *et al.* Diabetogenic effect of pentamidine: in vitro and in vivo studies in a patient with malignant insulinoma. *Am J Med* 1984; **77:** 41–6.
3. Stahl-Bayliss CM, *et al.* Pentamidine-induced hypoglycemia in patients with the acquired immune deficiency syndrome. *Clin Pharmacol Ther* 1986; **39:** 271–5.
4. Salmeron S, *et al.* Pentamidine and pancreatitis. *Ann Intern Med* 1986; **105:** 140–1.
5. Zuger A, *et al.* Pentamidine-associated fatal acute pancreatitis. *JAMA* 1986; **256:** 2383–5.
6. Sauleda J, *et al.* Probable pentamidine-induced acute pancreatitis. *Ann Pharmacother* 1994; **28:** 52–3.
7. Sattler FR, Waskin H. Pentamidine and fatal hypoglycemia. *Ann Intern Med* 1987; **107:** 789–90.
8. Herer B, *et al.* Pancreatitis associated with pentamidine by aerosol. *BMJ* 1989; **298:** 605.
9. Hart CC. Aerosolized pentamidine and pancreatitis. *Ann Intern Med* 1989; **111:** 691.
10. Fisch A. Diabetes mellitus in a patient with AIDS after treatment with pentamidine aerosol. *BMJ* 1990; **301:** 875.
11. Chen JP, *et al.* Diabetes after aerosolized pentamidine. *Ann Intern Med* 1991; **114:** 913–14.

Effects on the cardiovascular system. *Hypotension* is a problem with intravenous pentamidine, but can be reduced by infusing the dose over 60 minutes, when the incidence of hypotension appears to be similar to that with the intramuscular route.[1,2] Intravenous pentamidine has also been associated with *torsade de pointes*.[3-5]

1. Navin TR, Fontaine RE. Intravenous versus intramuscular administration of pentamidine. *N Engl J Med* 1984; **311:** 1701.

2. Helmick CG, Green JK. Pentamidine-associated hypotension and route of administration. *Ann Intern Med* 1985; **103:** 480.
3. Harel Y, *et al.* Pentamidine-induced torsade de pointes. *Pediatr Infect Dis J* 1993; **12:** 692–4.
4. Miller HC. Cardiac arrest after intravenous pentamidine in an infant. *Pediatr Infect Dis J* 1993; **12:** 694–6.
5. Zanetti LAF, Oliphant CM. Pentamidine-induced torsade de pointes. *Ann Pharmacother* 1994; **28:** 282–3.

Effects on the kidneys. In an analysis[1] of the adverse effects of parenteral pentamidine (see also under Incidence of Adverse Effects above), *nephrotoxicity* was often the most serious adverse reaction, although it was impossible to attribute it solely to pentamidine. Severe renal impairment occurred in 15 of 404 patients and contributed materially to 12 of 14 ensuing deaths. However, elevation of blood urea nitrogen was usually relatively mild and reversible in those patients who had normal pretreatment renal function and had received no other nephrotoxic agents. In two studies in patients with AIDS,[2,3] severe nephrotoxicity (increase in serum creatinine concentration of 0.5 mg per 100 mL) was reported in about 40% of patients. Analysis of risk factors suggested that the development of adverse reactions to parenteral pentamidine is correlated with the total dose received and the duration of treatment,[2,3] but not with the initial degree of renal function.[2] It has been observed that renal toxicity is more common when pentamidine is given intramuscularly, rather than intravenously, to AIDS patients with diarrhoea, suggesting that fluid status might have an important role.[4] There have been instances of renal failure occurring when pentamidine is inhaled as an aerosol for its local effect.[5,6]

1. Walzer PD, *et al.* Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; **80:** 83–93.
2. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; **25:** 1171–4.
3. O'Brien JG, *et al.* A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; **24:** 854–9.
4. Stehr-Green JK, Helmick CG. Pentamidine and renal toxicity. *N Engl J Med* 1985; **313:** 694–5.
5. Miller RF, *et al.* Acute renal failure after nebulised pentamidine. *Lancet* 1989; **i:** 1271–2.
6. Chapelon C, *et al.* Renal insufficiency with nebulised pentamidine. *Lancet* 1989; **ii:** 1045–6.

Effects on the nervous system. Paraesthesias have been reported with pentamidine therapy. Perioral numbness occurred in a patient soon after starting the third intravenous infusion of pentamidine for treatment of pneumocystis pneumonia and disappeared after the end of the infusion; numbness recurred with all subsequent pentamidine infusions.[1]

1. Milligan KS, Phillips DL. Perioral numbness associated with intravenous pentamidine administration. *Ann Pharmacother* 2007; **41:** 153–6.

Effects on the respiratory system. Although inhaled pentamidine has produced reactions that are normally associated with the parenteral route, the main problem after inhalation is bronchoconstriction;[1] it can be prevented by prior use of a bronchodilator. Acute eosinophilic pneumonia associated with nebulised pentamidine has been reported in a patient.[2] Concern has also been expressed at the risks to those who are with the patient at the time of inhalation and are exposed to nebulised pentamidine.[3-5]

1. Smith DE, *et al.* Reversible bronchoconstriction with nebulised pentamidine. *Lancet* 1988; **ii:** 905.
2. Dupon M, *et al.* Acute eosinophilic pneumonia induced by inhaled pentamidine isethionate. *BMJ* 1993; **306:** 109.
3. McDiarmid MA, Jacobson-Kram D. Aerosolised pentamidine and public health. *Lancet* 1989; **ii:** 863–4.
4. Thomas SHL, *et al.* Aerosolised pentamidine. *Lancet* 1989; **ii:** 1284.
5. Smaldone GC, *et al.* Detection of inhaled pentamidine in health care workers. *N Engl J Med* 1991; **325:** 891–2.

Precautions

Pentamidine should be used under close supervision and great care is necessary if it is used in patients suffering from any condition likely to be exacerbated by its adverse effects. The CSF should be checked for signs of CNS involvement before giving pentamidine for trypanosomiasis, since it is unlikely to be effective in such cases. Patients should remain supine while it is given and their blood pressure should be monitored. Kidney and liver function, blood-glucose concentrations, blood and platelet counts, and other parameters indicative of developing toxicity, such as serum-calcium concentrations and the ECG, should also be assessed regularly during courses of treatment with pentamidine.

Patients with a history of asthma or smoking may be at increased risk of cough and bronchospasm during inhalation of nebulised pentamidine. Symptoms may be controlled by giving a bronchodilator before pentamidine. Pentamidine solution should not be mixed with other drugs nor should a bronchodilator be given in the same nebuliser. Extrapulmonary *Pneumocystis jirovecii* infections may occur in patients given nebulised pentamidine and should be considered in patients with unexplained signs and symptoms. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to pentamidine.

Interactions

Use of pentamidine with other nephrotoxic drugs such as amphotericin B or foscarnet should preferably be avoided. Extreme caution is also necessary if pentamidine is given with other drugs, such as foscarnet, that can cause hypocalcaemia. There is an increased risk of ventricular arrhythmias if pentamidine is given with drugs which prolong the QT interval such as amiodarone, levacetylmethadol, or terfenadine. There may be an increased risk of pancreatitis when intravenous pentamidine is used with didanosine or zalcitabine and such combinations should be avoided.

Pharmacokinetics

After intravenous doses of the isetionate, pentamidine is rapidly distributed to body tissues and this is followed by a prolonged elimination phase. Elimination half-lives of 6 hours after intravenous infusion and 9 hours after intramuscular injection have been cited, but probably represent an intermediate value, and terminal elimination half-lives of between several days and weeks have been reported. During repeated dosing accumulation is believed to occur, particularly in the liver and kidneys, and only small concentrations of pentamidine are found in the urine.

Distribution to the lung is relatively poor after injection. Systemic absorption after inhalation is reported to result in peak plasma concentrations of 5 to 10% of those after parenteral use, and there have been a few reports of systemic adverse effects. Particle or droplet size appears to be important in achieving adequate pulmonary distribution.

◊ References.

1. O'Doherty MJ, *et al.* Differences in relative efficiency of nebulisers for pentamidine administration. *Lancet* 1988; **ii:** 1283–6.
2. Simonds AK, *et al.* Aerosolised pentamidine. *Lancet* 1989; **i:** 221–2.
3. Baskin MI, *et al.* Regional deposition of aerosolized pentamidine: effects of body position and breathing pattern. *Ann Intern Med* 1990; **113:** 677–83.
4. Bronner U, *et al.* Pentamidine concentrations in plasma, whole blood and cerebrospinal fluid during treatment of Trypanosoma gambiense in Côte d'Ivoire. *Trans R Soc Trop Med Hyg* 1991; **85:** 608–11.
5. Lidman C, *et al.* Plasma pentamidine concentrations vary between individuals with Pneumocystis carinii pneumonia and the drug is actively secreted by the kidney. *J Antimicrob Chemother* 1994; **33:** 803–10.
6. Bronner U, *et al.* Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with Trypanosoma gambiense sleeping sickness. *Br J Clin Pharmacol* 1995; **39:** 289–95.
7. Conte JE, Golden JA. Intrapulmonary and systemic pharmacokinetics of aerosolized pentamidine used for prophylaxis of Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus. *J Clin Pharmacol* 1995; **35:** 1166–73.

Renal impairment. In a study[1] of patients with normal renal function or on haemodialysis, renal clearance of pentamidine during the 24 hours after intravenous use was 2.1% of the plasma clearance in those with normal renal function, suggesting that pentamidine elimination would be largely unaffected by renal impairment. In those with end-stage renal disease on haemodialysis the terminal elimination half-life after a single dose was prolonged to about 75 hours, compared with 30 hours in the patients with normal renal function, but the volumes of distribution and area under the concentration-time curve were not significantly different. In patients with normal or mildly impaired renal function who had received between 12 and 21 doses, the terminal elimination half-life after the final dose was about 12 days and pentamidine was still detectable in the plasma after 6 weeks. There was evidence of accumulation of pentamidine during repeated daily dosing.

1. Conte JE. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. *J Infect Dis* 1991; **163:** 169–75.

Uses and Administration

Pentamidine, an aromatic diamidine derivative, is an antiprotozoal used in the treatment of the early stages of African trypanosomiasis, especially *Trypanosoma brucei gambiense* infections, and in some forms of leishmaniasis. It is also used in the treatment and prophylaxis of pneumocystis pneumonia. It may act by several mechanisms, including interference with protozoal DNA and folate transformation and by inhibition of RNA and protein synthesis.

Pentamidine has been given as the isetionate or mesilate salt, but the isetionate is the only form now available in most countries. There is considerable confusion in the literature regarding the dosage of pentamidine since it is often not clear whether doses are being expressed in terms of pentamidine base, the isetionate salt, or the mesilate salt. In general it would appear that when the isetionate is used doses are expressed in terms of pentamidine isetionate, whereas when the mesilate is used doses are expressed in terms of pentamidine base. Pentamidine isetionate 4 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base; pentamidine mesilate 3.6 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base.

Pentamidine isetionate is given by deep intramuscular injection or by slow intravenous infusion over at least 60 minutes; direct intravenous injection must be avoided. Patients should be lying down. The mesilate has usually been given intramuscularly.

In the treatment of early **African trypanosomiasis** due to *T. b. gambiense*, pentamidine isetionate 4 mg/kg may be given daily or on alternate days by intramuscular injection or intravenous infusion to a total of 7 to 10 doses. Pentamidine is not effective in trypanosomiasis with CNS involvement, but 2 doses of pentamidine may be given in late-stage *T. b. gambiense* infection before starting treatment with melarsoprol or eflornithine.

In the treatment of visceral **leishmaniasis**, and of mucocutaneous leishmaniasis due to *Leishmania braziliensis* or *L. aethiopica* that have not responded to antimonials, pentamidine isetionate 4 mg/kg may be given, preferably intramuscularly three times weekly, for 5 to 25 weeks or longer. An alternative regimen in visceral leishmaniasis is to give 3 to 4 mg/kg on alternate days to a maximum of 10 injections; the course may need to be repeated. In cutaneous leishmaniasis due to *L. aethiopica* or *L. guyanensis*, pentamidine isetionate 3 to 4 mg/kg may be given, preferably intramuscularly once or twice weekly, until the condition resolves. A weekly dose of 3 to 4 mg/kg is also used for diffuse cutaneous leishmaniasis due to *L. aethiopica* and should be continued for at least 4 months after parasites are no longer detectable on skin smears.

In the treatment of **pneumocystis pneumonia**, pentamidine isetionate 4 mg/kg is given once daily for 14 days or longer, by intramuscular injection or preferably slow intravenous infusion. Pentamidine isetionate is given by inhalation through a nebuliser to prevent pneumocystis pneumonia in HIV-positive patients in a dose of 300 mg once every 4 weeks; in those who cannot tolerate this dose 150 mg every 2 weeks may be used. It has also occasionally been used by this route for treating mild to moderate *P. jirovecii* infection in a dose of 600 mg daily for 3 weeks. Nebuliser design can affect the droplet size delivered and hence the amount of pentamidine reaching sites of action within the lungs. The optimal particle size is 1 to 2 μm. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to the drug.

Administration in renal impairment. Since renal clearance accounts for only a small proportion of pentamidine elimination, dosage adjustment is not generally considered necessary for mild to moderate degrees of renal impairment. UK licensed product information recommends dosage reductions in patients with pneumocystis pneumonia who have a creatinine clearance of less than 10 mL/minute. In patients with life-threatening disease the recommended dose of 4 mg/kg daily should be given for 7 to 10 days and then on alternate days for the remainder of the 14-dose course. In less severe disease the suggested dose is 4 mg/kg on alternate days for 14 doses.

Amoebic infections. ***ACANTHAMOEBA INFECTIONS.*** Pentamidine was used to treat disseminated *Acanthamoeba* infection (p.822) without evidence of CNS involvement in 2 immunocompromised patients.[1,2] It is unlikely that pentamidine would be effective in infections involving the CNS.

1. Slater CA, *et al.* Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; **331:** 85–7.
2. Murakawa GJ, *et al.* Disseminated Acanthamoeba in patients with AIDS: a report of five cases and a review of the literature. *Arch Dermatol* 1995; **131:** 1291–6.

Babesiosis. Pentamidine has been tried for babesiosis (p.823), but while some patients showed clinical improvements,[1-3] the efficacy and safety of pentamidine in this infection has been questioned.[4]

1. Francioli PB, *et al.* Response of babesiosis to pentamidine therapy. *Ann Intern Med* 1981; **94:** 326–30.
2. Raoult D, *et al.* Babesiosis, pentamidine, and cotrimoxazole. *Ann Intern Med* 1987; **107:** 944.
3. Clarke CS, *et al.* Babesiosis: under-reporting or case-clustering? *Postgrad Med J* 1989; **65:** 591–3.
4. Teutsch SM, Juranek DD. Babesiosis. *Ann Intern Med* 1981; **95:** 241.

Leishmaniasis. Pentamidine has been used in the treatment of visceral leishmaniasis (p.824) both alone and with antimonials in patients who have failed to respond to antimonials alone.[1,2] It has also been tried for long-term secondary prophylaxis in patients with HIV infection.[3] Cutaneous leishmaniasis due to *L. guyanensis* is usually treated with pentamidine to reduce the risk of dissemination;[1] beneficial results in patients infected with *L. infantum*, *L. major*, or *L. tropica* have also been reported.[4] Lesions due to *L. aethiopica* may also respond to pentamidine, but can be left to heal spontaneously since the risk of diffuse cutaneous involvement is small.[1] Diffuse cutaneous or mucocutaneous disease which is unresponsive to antimonials may respond to pentamidine.[1]

For mention of the use of pentamidine with paromomycin to treat visceral leishmaniasis in an HIV-infected patient, see p.844.

1. WHO. *WHO model formulary.* Geneva: WHO, 2004.
2. Baily GG, Nandy A. Visceral leishmaniasis: more prevalent and more problematic. *J Infect* 1994; **29:** 241–7.
3. Pérez-Molina JA, *et al.* Pentamidine isethionate as secondary prophylaxis against visceral leishmaniasis in HIV-positive patients. *AIDS* 1996; **10:** 237–8.
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Pneumocystis pneumonia. In the treatment of pneumocystis pneumonia (p.521) intravenous pentamidine is generally reserved for patients with moderate to severe disease who do not respond to, or cannot tolerate, co-trimoxazole. Co-trimoxazole with pentamidine is no more effective than pentamidine alone in these patients and is potentially more toxic than either drug.[1] Inhaled pentamidine has occasionally been suggested for mild to moderate infection, but is now generally only used for prophylaxis. However, patients given inhaled pentamidine may be prone to extrapulmonary *Pneumocystis* infections.[2,3]

In both primary and secondary prophylaxis of pneumocystis pneumonia in immunocompromised patients, co-trimoxazole is preferred to inhaled pentamidine. Comparative studies have shown that, in the short term, inhaled pentamidine has been less effective than co-trimoxazole[4,5] and no more effective than another common prophylactic drug, dapsone.[6,7] In addition, both co-trimoxazole and dapsone (given with pyrimethamine) also provide protection against toxoplasmosis and extrapulmonary pneumocystis infections. However, inhaled pentamidine is better tolerated than either of these, and studies have suggested that in the long term the efficacy of the three drugs is comparable,[8,9] at least in patients with CD4+ T lymphocyte counts of more than 100 cells/microlitre. Increasing the dose of pentamidine from 300 mg every four weeks to 300 mg every two weeks[10,11] or 600 mg every week[12] may improve efficacy further. Intermittent parenteral dosage of pentamidine has been used when the more usual drugs cannot be given.[13]

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4. Schneider MME, *et al.* A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992; **327:** 1836–41.
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6. Girard P-M, *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; **328:** 1514–20.
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8. Bozzette SA, *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; **332:** 693–9.
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10. Kronawitter U, *et al.* Low incidence of Pneumocystis carinii pneumonia in HIV patients receiving 300 mg pentamidine aerosol every 2 weeks. *Clin Investig* 1992; **70:** 1089–91.
11. Rizzardi GP, *et al.* Better efficacy of twice-monthly than monthly aerosolised pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with AIDS: an Italian multicentric randomised controlled trial. *J Infect* 1995; **31:** 99–105.
12. Ong ELC, *et al.* Efficacy and effects on pulmonary function tests of weekly 600 mg aerosol pentamidine as prophylaxis against Pneumocystis carinii pneumonia. *Infection* 1992; **20:** 136–9.
13. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5108.pdf (accessed 27/05/05)

African trypanosomiasis. Pentamidine is used for the haematolymphatic phase of African trypanosomiasis caused by *Trypanosoma brucei gambiense* (p.827), and as an adjunct to other treatment for the meningoencephalitic stage of the infection.[1] It is reported to be less effective against *T. b. rhodesiense* and in some areas resistance of *T. b. gambiense* to pentamidine is increasing. Pentamidine has been used with suramin for *T. b. gambiense* infections but this has not been shown to be clinically superior to pentamidine alone.[2]

1. WHO. Control and surveillance of African trypanosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 881* 1998.
2. Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg* 1996; **90:** 183–6.

Preparations

BP 2008: Pentamidine Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Pentacarinat; ***Belg.:*** Pentacarinat; ***Braz.:*** Pentacarinat; Sideron†; ***Canad.:*** Pentacarinat†; ***Denm.:*** Pentacarinat; ***Fin.:*** Pentacarinat†; ***Fr.:*** Pentacarinat; ***Ger.:*** Pentacarinat; ***Gr.:*** Pentacarinate; Pentam; ***Irl.:*** Pentacarinat; ***Israel:*** Pentacarinat†; ***Ital.:*** Pentacarinat; ***Neth.:*** Pentacarinat; ***NZ:*** Pentacarinat; ***Port.:*** Pentacarinat†; Pentamina; ***Spain:*** Pentacarinat; ***Swed.:*** Pentacarinat; ***Switz.:*** Pentacarinat; ***Thai.:*** Pentacarinat; ***UK:*** Pentacarinat; ***USA:*** NebuPent; Pentacarinat; Pentam.

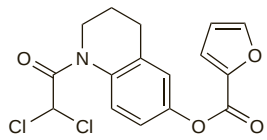
Quinfamide *(USAN, rINN)*

Quinfamida; Quinfamidum; Win-40014. 1-(Dichloroacetyl)-1,2,3,4-tetrahydroquinolin-6-ol 2-furoic acid ester.

Хинфамид

$C_{16}H_{13}Cl_2NO_4$ = 354.2.

CAS — 62265-68-3.



Profile

Quinfamide is a luminal amoebicide. It is given orally for intestinal amoebiasis in a dose of 300 mg, either as a single dose or as three divided doses over 24 hours.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Amefin; Amefur; Amenox; Amofur; Bisidim; Celemin; Doffler; Falacid; Luminovag; Protosin; Quocel; Serphamida.

Multi-ingredient: ***Mex.:*** Amibriz†; Amoebriz; Oxal; Vermox-Plus.

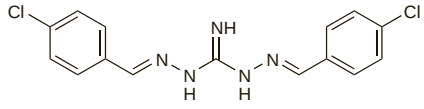
Robenidine Hydrochloride *(BANM, USAN, rINNM)*

CL-78116; Hidrocloruro de robenidina; Robénidine, Chlorhydrate de; Robenidini Hydrochloridum; Robenzidene Hydrochloride. 1,3-Bis(4-chlorobenzylideneamino)guanidine hydrochloride.

Робенидина Гидрохлорид

$C_{15}H_{13}Cl_2N_5$,HCl = 370.7.

CAS — 25875-51-8 (robenidine); 25875-50-7 (robenidine hydrochloride).



(robenidine)

Profile

Robenidine is an antiprotozoal used as the hydrochloride in veterinary practice for the prevention of coccidiosis in poultry and rabbits.

Ronidazole *(BAN, USAN, pINN)*

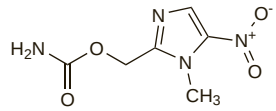
Ronidazol; Ronidazolum. (1-Methyl-5-nitroimidazol-2-yl)methyl carbamate.

Ронидазол

$C_6H_8N_4O_4$ = 200.2.

CAS — 7681-76-7.

ATC Vet — QP51AA08.



Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Ronidazole). A white to yellowish-brown, odourless or almost odourless powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. Protect from light.

Profile

Ronidazole is a 5-nitroimidazole antiprotozoal that is used in veterinary practice for the control of trichomoniasis in cage birds and pigeons. It has also been added to turkey feeding stuffs and has been used for the control of swine dysentery.

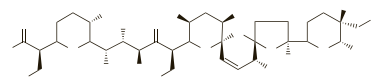
Salinomycin Sodium *(BANM, rINNM)*

AHR-3096 (salinomycin); K-364 (salinomycin); K-748364A (salinomycin); Natrii Salinomycinum; Salinomicina sódica; Salinomycine Sodique. Sodium (2*R*)-2-{(2*R*,5*S*,6*R*)-6-[(1*S*,2*S*,3*S*,5*R*)-5-{(2*S*,5*S*,7*R*,9*S*,10*S*,12*R*,15*R*)-2-[(2*R*,5*R*,6*S*)-5-ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl]-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl}-2-hydroxy-1,3-dimethyl-4-oxoheptyl]tetrahydro-5-methylpyran-2-yl}butyrate.

Натрий Салиномицин

$C_{42}H_{69}NaO_{11}$ = 773.0.

CAS — 53003-10-4 (salinomycin); 55721-31-8 (salinomycin sodium).



(salinomycin)

Profile

Salinomycin, an antibiotic produced by *Streptomyces albus*, is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor in pigs.

Secnidazole *(BAN, rINN)*

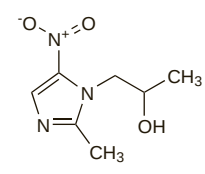
PM-185184; 14539-RP; RP-14539; Secnidazol; Secnidazolum; Seknidazol. 1-(2-Methyl-5-nitroimidazol-1-yl)propan-2-ol.

Секнидазол

$C_7H_{11}N_3O_3$ = 185.2.

CAS — 3366-95-8.

ATC — P01AB07.



Profile

Secnidazole is a 5-nitroimidazole derivative with properties similar to those of metronidazole (p.837), apart from a much longer plasma half-life of 20 hours or more. It is used in the treatment of amoebiasis, giardiasis, and trichomoniasis.

Secnidazole is given orally, usually as a single dose of 2 g in adults or 30 mg/kg in children. In invasive (hepatic) amoebiasis