sion immediately before use. The usual initial dose in adults and children 2 years of age and older is 20 mg/kg once daily, taken on an empty stomach at least 30 minutes before food. Serum ferritin should be monitored monthly and the dose should be adjusted every 3 to 6 months as necessary. The maximum recommended dose is 30 mg/kg daily.

◊ References.

1. VanOrden HE, Hagemann TM. Deferasirox—an oral agent for chronic iron overload. *Ann Pharmacother* 2006; **40:** 1110–17.
2. Stumpf JL. Deferasirox. *Am J Health-Syst Pharm* 2007; **64:** 606–16.
3. Yang LPH, *et al*. Deferasirox: a review of its use in the management of transfusional chronic iron overload. *Drugs* 2007; **67:** 2211–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Exjade; ***Austral.:*** Exjade; ***Chile:*** Exjade; ***Cz.:*** Exjade; ***Fr.:*** Exjade; ***Gr.:*** Exjade; ***Hung.:*** Exjade; ***Indon.:*** Exjade; ***Malaysia:*** Exjade; ***NZ:*** Exjade; ***UK:*** Exjade; ***USA:*** Exjade.

Deferiprone *(BAN, rINN)*

CP-20; Deferipron; Deferiprona; Défériprone; Deferiproni; Deferipronum; Dimethylhydroxypyridone; L1. 1,2-Dimethyl-3-hydroxypyrid-4-one; 3-Hydroxy-1,2-dimethyl-4-pyridone.

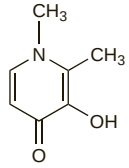
Деферипрон

$C_7H_9NO_2$ = 139.2.

CAS — 30652-11-0.

ATC — V03AC02.

ATC Vet — QV03AC02.



Adverse Effects and Precautions

Deferiprone has been shown to cause neutropenia and should not be used in neutropenic patients; the neutrophil count should be monitored weekly and treatment should be stopped if neutropenia develops. Agranulocytosis has also occurred. Patients should be advised to seek immediate medical attention if symptoms indicative of infection such as fever, sore throat, or flu-like symptoms occur.

Gastrointestinal disorders such as diarrhoea, nausea, vomiting, and abdominal pain are common during deferiprone treatment and may require a temporary reduction in dose. A reddish-brown discoloration of the urine is also common. Other adverse effects that have been reported include arthralgia and increased liver enzymes. Deferiprone may reduce plasma-zinc concentrations and zinc supplements may be required.

Deferiprone is teratogenic in *animals* and should not be used during pregnancy. Women of child-bearing potential should be advised to use contraceptive measures during treatment with deferiprone.

Caution is advised in patients with hepatic or renal impairment.

Effects on the blood. Agranulocytosis, in some cases fatal, has been reported in association with deferiprone use.[1,2]

1. Henter J-I, Karlén J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. *Blood* 2007; **109:** 5157–9.
2. Anonymous. Deferiprone: agranulocytosis and neurological disorders. *Prescrire Int* 2007; **16:** 72.

Overdosage. Neurological disorders were reported by the manufacturer and the French pharmacovigilance authorities in 2 children aged 7 and 9 who had been treated with deferiprone doses at 2⁄ times the highest recommended dose of 100 mg/kg daily. The children were treated for 1 and 2 years, respectively, and developed nystagmus, gait disorders, ataxia, dystonia, and, in one case, psychomotor retardation. These disorders gradually improved after deferiprone was stopped.[1]

1. Agence française de sécurité sanitaire des produits de santé/Laboratoires Chiesi, France. Risque d'agranulocytoses fatales et de troubles neurologiques lors de l'utilisation de Ferriprox (déféripirone) (issued 1st September, 2006). Available at: http://agmed.sante.gouv.fr/htm/10/filltrpsc/lp060901.pdf (accessed 27/09/07)

Interactions

Deferiprone chelates trivalent metal ions and could interact with aluminium-containing preparations; it should not be given with aluminium-containing antacids. Due to the risk of additive toxicity, use with drugs that may cause neutropenia or agranulocytosis is not recommended.

Pharmacokinetics

Deferiprone is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring 45 to 60 minutes after an oral dose; absorption may be slowed in the presence of food and peak serum concentrations may be reduced. Deferiprone is metabolised to an inactive glucuronide metabolite and is excreted primarily in the urine, mainly as the metabolite and the iron-deferiprone complex, with a small amount of unchanged drug. The elimination half-life is about 2 to 3 hours.

Uses and Administration

Deferiprone is an orally active iron chelator used in the treatment of iron overload in patients with thalassaemia for whom desferrioxamine is unsuitable or ineffective. It may be given by mouth in doses of 25 mg/kg three times daily. Doses above 100 mg/kg daily are not recommended. For use in children, see Administration in Children, below.

◊ Reviews.

1. Barman Balfour JA, Foster RH. Deferiprone: a review of its clinical potential in iron overload in β-thalassaemia major and other transfusion-dependent diseases. *Drugs* 1999; **58:** 553–78.
2. Kontoghiorghes GJ, *et al*. Benefits and risks of deferiprone in iron overload in thalassaemia and other conditions: comparison of epidemiological and therapeutic aspects with deferoxamine. *Drug Safety* 2003; **26:** 553–84.
3. Hoffbrand AV. Deferiprone therapy for transfusional iron overload. *Best Pract Res Clin Haematol* 2005; **18:** 299–317.
4. Piga A, *et al*. Deferiprone: new insight. *Ann N Y Acad Sci* 2005; **1054:** 169–74.

Administration in children. UK licensed product information states that there are limited data on the use of deferiprone in children between 6 and 10 years of age, and no data on use in children below 6. Australian licensed product information states that limited data exist for children between the ages of 2 and 10 but that the effects of deferiprone on growth are unknown. Licensed doses in children are calculated by weight on the same basis as adults (see Uses and Administration, above).

Thalassaemia. Patients with thalassaemia receiving regular blood transfusions commonly develop iron overload requiring use of iron chelators. Deferiprone was developed as an oral alternative to desferrioxamine, but its role has been controversial. See Thalassaemia under Uses of Desferrioxamine, p.1442, for further information.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferriprox; ***Austral.:*** Ferriprox; ***Belg.:*** Ferriprox; ***Braz.:*** Ferriprox; ***Cz.:*** Ferriprox; ***Denm.:*** Ferriprox; ***Fin.:*** Ferriprox; ***Fr.:*** Ferriprox; ***Ger.:*** Ferriprox; ***Gr.:*** Ferriprox; Kelfer; ***Hong Kong:*** Ferriprox; ***India:*** Kelfer; ***Irl.:*** Ferriprox†; ***Ital.:*** Ferriprox; ***Malaysia:*** Ferriprox; Kelfer; ***Neth.:*** Ferriprox; ***Port.:*** Ferriprox; ***Spain:*** Ferriprox; ***Swed.:*** Ferriprox; ***Switz.:*** Ferriprox; ***Turk.:*** Ferriprox; ***UK:*** Ferriprox.

Desferrioxamine Mesilate *(BANM)*

Deferoxamine Mesilate *(pINNM)*; Ba-33112; Ba-29837 (desferrioxamine hydrochloride); Deferoksamiinimesilaatti; Deferoksamin Mezilat; Deferoksamino mesilatas; Déferoxamine, Mésilate de; Déféroxamine, mésilate de; Deferoxamine Mesylate *(USAN)*; Deferoxamini mesilas; Deferoxaminmesilat; Deferoxaminmesylát; Deferoxamin-mezilát; Desferrioksamin Mesilat; Desferrioxamine Mesylate; Desferrioxamine Methanesulphonate; Mesilato de deferoxamina; NSC-527604 (desferrioxamine). 30-Amino-3,14,25-trihydroxy-3,9,14,20,25-penta-azatriacontane-2,10,13,21,24-pentaone methanesulphonate; *N*′-{5-[(4-{[5-(Acetylhydroxyamino)pentyl]amino}-1,4-dioxobutyl)hydroxyamino]pentyl}-*N*-(5-aminopentyl)-*N*-hydroxy-butanediamide monomethanesulphonate.

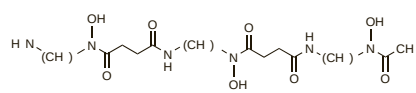
Дефероксамина Мезилат

$C_{25}H_{48}N_6O_8,CH_3SO_3H$ = 656.8.

CAS — 70-51-9 (desferrioxamine); 138-14-7 (desferrioxamine mesilate); 1950-39-6 (desferrioxamine hydrochloride).

ATC — V03AC01.

ATC Vet — QV03AC01.



(desferrioxamine)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Deferoxamine Mesilate; Desferrioxamine Mesilate BP 2008). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol. A freshly prepared 10% solution in water has a pH of 3.7 to 5.5. Store at 2° to 8°. Protect from light.
USP 31 (Deferoxamine Mesylate). A white to off-white powder. Freely soluble in water; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Incompatibility. Licensed product information states that desferrioxamine solutions are incompatible with heparin.

Adverse Effects and Treatment

Rapid intravenous injection of desferrioxamine may cause flushing, urticaria, hypotension, and shock. Local pain may occur with subcutaneous or intramuscular injections and pruritus, erythema, and swelling have occurred after prolonged subcutaneous use. Gastrointestinal disorders, dysuria, fever, allergic skin rashes, tachycardia, cardiac arrhythmias, convulsions, and leg cramps have been reported. Visual disturbances, including retinal changes, and hearing loss may occur and may be reversible if desferrioxamine is withdrawn. Cataract formation has also been reported. Desferrioxamine therapy may retard growth in very young children.

The adverse effects of desferrioxamine generally respond to dosage reduction. In acute overdosage desferrioxamine may be removed by haemodialysis.

◊ Reviews of the adverse effects of desferrioxamine.

1. Bentur Y, *et al.* Deferoxamine (desferrioxamine): new toxicities for an old drug. *Drug Safety* 1991; **6:** 37–46.

Effects on the blood. A patient with end-stage renal disease developed reversible thrombocytopenia on 3 separate occasions after intravenous infusions of desferrioxamine for dialysis osteomalacia.[1] Acute fatal aplastic anaemia occurred in a 16-year-old girl with thalassaemia after high intravenous doses of desferrioxamine (80 mg/kg daily) for 20 days.[2]

1. Walker JA, *et al*. Thrombocytopenia associated with intravenous desferrioxamine. *Am J Kidney Dis* 1985; **6:** 254–6.
2. Sofroniadou K, *et al.* Acute bone marrow aplasia associated with intravenous administration of deferoxamine (desferrioxamine). *Drug Safety* 1990; **5:** 152–4.

Effects on the ears and eyes. Lens opacities, retinal pigmentary changes and other retinal abnormalities, and ocular disturbances including loss of colour vision, night blindness, decreased visual acuity, and field defects, have been reported in patients receiving long-term or high-dose treatment with desferrioxamine.[1-4] The incidence appears to be about 30%, although individual studies have reported widely differing rates; in 2 studies long-term use of desferrioxamine was associated with symptomatic or asymptomatic ocular changes in 4% (2 of 52)[5] and 66% (10 of 15)[6] of patients respectively.

Sensorineural hearing impairment has also been reported,[5,7-12] and in one study[13] was attributed to desferrioxamine in 29% of patients (22 of 75). Tinnitus has been reported in a few patients.[11,14]

The mechanism by which desferrioxamine causes neurotoxicity is unclear. Some studies[8,15] have found an association with dose, suggesting a direct toxic effect of desferrioxamine; other studies[6,16] have suggested that depletion of trace metals, particularly zinc or copper, may be involved. Both ophthalmic and auditory abnormalities can improve when desferrioxamine is withdrawn,[1,3,5-10] although sometimes the effects may be irreversible[17] or recovery may only be partial.[8,9] There has also been a report[18] of improvement following use of zinc supplements.

1. Davies SC, *et al.* Ocular toxicity of high-dose intravenous desferrioxamine. *Lancet* 1983; **ii:** 181–4.
2. Simon P, *et al.* Desferrioxamine, ocular toxicity, and trace metals. *Lancet* 1983; **ii:** 512–13.
3. Borgna-Pignatti C, *et al*. Visual loss in patient on high-dose subcutaneous desferrioxamine. *Lancet* 1984; **i:** 681.
4. Rubinstein M, *et al.* Ocular toxicity of desferrioxamine. *Lancet* 1985; **i:** 817–18.
5. Cohen A, *et al.* Vision and hearing during deferoxamine therapy. *J Pediatr* 1990; **117:** 326–30.
6. De Virgiliis S, *et al.* Depletion of trace elements and acute ocular toxicity induced by desferrioxamine in patients with thalassaemia. *Arch Dis Child* 1988; **63:** 250–5.
7. Guerin A, *et al.* Acute deafness and desferrioxamine. *Lancet* 1985; **ii:** 39.
8. Olivieri NF, *et al.* Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. *N Engl J Med* 1986; **314:** 869–73.
9. Barratt PS, Toogood IRG. Hearing loss attributed to desferrioxamine in patients with beta-thalassaemia major. *Med J Aust* 1987; **147:** 177–9.
10. Wonke B, *et al*. Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA. *Arch Dis Child* 1989; **64:** 77–82.
11. Porter JB, *et al.* Desferrioxamine ototoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. *Br J Haematol* 1989; **73:** 403–9.
12. Argiolu F, *et al*. Hearing impairment during deferoxamine therapy for thalassemia major. *J Pediatr* 1991; **118:** 826.
13. Chiodo AA, *et al*. Desferrioxamine ototoxicity in an adult transfusion-dependent population. *J Otolaryngol* 1997; **26:** 116–22.
14. Marsh MN, *et al.* Tinnitus in a patient with beta-thalassaemia intermedia on long-term treatment with desferrioxamine. *Postgrad Med J* 1981; **57:** 582–4.

15. Bentur Y, *et al.* Comparison of deferoxamine pharmacokinetics between asymptomatic thalassemic children and those exhibiting severe neurotoxicity. *Clin Pharmacol Ther* 1990; **47:** 478–82.
16. Pall H, *et al.* Ocular toxicity of desferrioxamine – an example of copper promoted auto-oxidative damage? *Br J Ophthalmol* 1989; **73:** 42–7.
17. Bene C, *et al.* Irreversible ocular toxicity from single "challenge" dose of deferoxamine. *Clin Nephrol* 1989; **31:** 45–8.
18. Pinna A, *et al.* Rapid recovery with oral zinc sulphate in deferoxamine-induced presumed optic neuropathy and hearing loss. *J Neuroophthalmol* 2001; **21:** 32–3.

Effects on growth rate. Growth retardation has been noted in thalassaemic children undergoing desferrioxamine therapy.[1,2] Growth retardation was related to dose[1,2] and inversely related to iron stores.[1] It was greater in those who started receiving desferrioxamine at the start of transfusion therapy at about 9 months old than in those who started desferrioxamine once iron accumulation was established, after about 3 years. A sharp increase in growth velocity was reported in 15 patients with low ferritin levels after a 50% reduction in desferrioxamine dose.[1]

1. Piga A, *et al.* High-dose desferrioxamine as a cause of growth failure in thalassaemic patients. *Eur J Haematol* 1988; **40:** 380–1.
2. De Virgiliis S, *et al.* Deferoxamine-induced growth retardation in patients with thalassemia major. *J Pediatr* 1988; **113:** 661–9.

Effects on the kidneys. Intensive treatment with intravenous infusions of desferrioxamine has been associated[1,2] with acute decreases in renal function, and it has been suggested[3] that nephrotoxicity could be related to the high doses used; acute renal failure has also been reported[4,5] after intravenous overdosage of desferrioxamine. However, other studies[6,7] have also found reductions in renal function associated with more usual subcutaneous dosage regimens.

1. Batey R, *et al.* Acute renal insufficiency occurring during intravenous desferrioxamine therapy. *Scand J Haematol* 1979; **22:** 277–9.
2. Koren G, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1989; **143:** 1077–80.
3. Li Volti S, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1990; **144:** 1069–70.
4. Cianciulli P, *et al.* Acute renal failure occurring during intravenous desferrioxamine therapy: recovery after haemodialysis. *Haematologica* 1992; **77:** 514–15.
5. Prasannan L, *et al.* Acute renal failure following deferoxamine overdose. *Pediatr Nephrol* 2003; **18:** 283–5.
6. Koren G, Bentur Y. Acute changes in renal function associated with deferoxamine. *Am J Dis Child* 1990; **144:** 1070.
7. Cianciulli P, *et al.* Early detection of nephrotoxic effects in thalassemic patients receiving desferrioxamine therapy. *Kidney Int* 1994; **46:** 467–70.

Effects on the lungs. Pulmonary complications, including fatal acute respiratory distress syndrome, have been reported in patients given prolonged or high-dose intravenous desferrioxamine. A pulmonary syndrome with tachypnoea, hypoxaemia, reduced pulmonary function, and evidence of diffuse interstitial fibrosis and inflammation, has been reported[1,2] with high doses, possibly associated with a hypersensitivity reaction. There has also been a report[3] of fatal acute respiratory distress syndrome in 4 patients given intravenous desferrioxamine for 65 to 92 hours; toxicity was attributed to the prolonged infusion since no pulmonary complications had been noted with desferrioxamine given for less than 24 hours. Subsequent correspondence, however, suggested alternative explanations for the pulmonary injury including the use of doses above the daily maximum,[4] as well as inadequate desferrioxamine therapy.[5]

1. Freedman MH, *et al.* Pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine infusions. *Am J Dis Child* 1990; **144:** 565–9.
2. Scanderbeg AC, *et al.* Pulmonary syndrome and intravenous high-dose desferrioxamine. *Lancet* 1990; **336:** 1511.
3. Tenenbein M, *et al.* Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. *Lancet* 1992; **339:** 699–701.
4. Macarol V, Yawalkar SJ. Desferrioxamine in acute iron poisoning. *Lancet* 1992; **339:** 1601.
5. Shannon M. Desferrioxamine in acute iron poisoning. *Lancet* 1992; **339:** 1601.

Effects on the skin. Desferrioxamine may be used in the management of porphyria cutanea tarda (see p.1448). However, lesions resembling porphyria cutanea tarda developed in 3 patients during long-term therapy with desferrioxamine for aluminium toxicity.[1] The lesions worsened on exposure to sun and resolved when treatment was completed. It was also possible that the lesions were associated with aluminium accumulation. Alopecia was noted in 1 patient but an association with desferrioxamine could not be established.

1. McCarthy JT, *et al.* Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med* 1990; **74:** 257–76.

Hypersensitivity. Individual cases of anaphylactoid reactions have been reported with desferrioxamine given by various parenteral routes, and desensitisation has been carried out successfully in some patients.[1-4] Immunological studies have suggested that the reaction may be pseudo-allergic in nature;[2-4] 4 patients who were unable to tolerate subcutaneous desferrioxamine due to severe hypersensitivity reactions were successfully treated with high-dose intravenous therapy.[5]

Effects on the lungs have also been attributed to hypersensitivity (see above).

1. Miller KB, *et al.* Rapid desensitisation for desferrioxamine anaphylactic reaction. *Lancet* 1981; **i:** 1059.
2. Bousquet J, *et al.* Rapid desensitisation for desferrioxamine anaphylactoid reactions. *Lancet* 1983; **ii:** 859–60.
3. Patriarca G, *et al.* Successful desensitization of a child with desferrioxamine hypersensitivity. *J Investig Allergol Clin Immunol* 1995; **5:** 294–5.
4. La Rosa M, *et al.* Desensitization treatment for anaphylactoid reactions to desferrioxamine in a pediatric patient with thalassemia. *J Allergy Clin Immunol* 1996; **97:** 127–8.
5. Lombardo T, *et al.* High-dose intravenous desferrioxamine (DFO) delivery in four thalassemic patients allergic to subcutaneous DFO administration. *Am J Hematol* 1996; **51:** 90–2.

Precautions

Desferrioxamine should be used with caution in patients with renal impairment since the metal complexes are excreted by the kidneys; in those with severe renal impairment dialysis increases elimination. The desferrioxamine-iron complex may colour the urine reddish-brown.

Desferrioxamine may exacerbate aluminium-related encephalopathy and precipitate seizures. Prophylactic treatment with antiepileptics such as clonazepam has been suggested for patients judged to be at risk.

An increased susceptibility to infection, particularly with *Yersinia* species, has been reported in patients with iron overload treated with desferrioxamine. Severe fungal infections have also been reported, mainly in patients undergoing dialysis. If infection is suspected, treatment with desferrioxamine should be stopped and appropriate antimicrobial treatment given.

Skeletal fetal anomalies have occurred in *animals*.

The urinary excretion of iron should be regularly monitored during treatment and periodic ophthalmological and audiological examinations are recommended for patients on long-term therapy. Monitoring of cardiac function is also recommended for patients receiving combined treatment with ascorbic acid (see also under Interactions, below).

Inappropriately high dosage in children with low ferritin levels may retard growth and therefore regular checks on height and weight are recommended for children.

Aluminium encephalopathy. Desferrioxamine may be used in the management of aluminium-associated encephalopathy, but has also been associated with precipitation or exacerbation of dementia,[1-3] with some fatal outcomes,[1] in dialysis patients with aluminium overload. It has been suggested[2] that the effect could be dose related. Desferrioxamine mobilises stored aluminium and may therefore increase plasma-aluminium concentrations, leading to toxicity. Use of a low dose of desferrioxamine (for example, 10 mg/kg) shortly before dialysis, in addition to charcoal haemoperfusion, has been recommended.[1] However, exacerbation of aluminium encephalopathy has also been reported[3] after the low dose of 500 mg twice weekly.

1. Sherrard DJ, *et al.* Precipitation of dialysis dementia by deferoxamine treatment of aluminum related bone disease. *Am J Kidney Dis* 1988; **12:** 126–30.
2. McCauley J, Sorkin I. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; **4:** 110–14.
3. Lillevang ST, Pedersen FB. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; **4:** 676.

Diagnostic tests. *In vitro* and *animal* studies[1] have suggested that desferrioxamine could interfere with estimations of total iron-binding capacity. It may also interfere with colorimetric iron assays.

Desferrioxamine also binds gallium and has been reported[2-4] to distort the results of gallium-67 imaging studies.

1. Bentur Y, *et al.* Misinterpretation of iron-binding capacity in the presence of deferoxamine. *J Pediatr* 1991; **118:** 139–42.
2. Nagamachi S, *et al.* Gallium-67 scintigraphy in patients with hemochromatosis treated by deferoxamine. *Ann Nucl Med* 1988; **2:** 35–9.
3. Baker DL, Manno CS. Rapid excretion of gallium-67 isotope in an iron-overloaded patient receiving high-dose intravenous deferoxamine. *Am J Hematol* 1988; **29:** 230–2.
4. Brown SJ, *et al.* Altered biodistribution of gallium-67 in a patient with aluminum toxicity treated with desferoxamine. *J Nucl Med* 1990; **31:** 115–17.

Infection susceptibility. *Yersinia enterocolitica* is one of the most iron-dependent of all microbes and the risk of infection is increased in patients with iron overload. Use of exogenous iron-binding compounds (siderophores) such as desferrioxamine, may increase the ability of *Y. enterocolitica* to take up iron and may contribute to the increased risk of infection. Infections due to *Y. enterocolitica* (p.174) have been reported in patients receiving desferrioxamine for acute iron overdosage[1] or for chronic iron overload.[2-5] Severe infection with *Y. pseudotuberculosis* has also been reported in a thalassaemic patient on long-term desferrioxamine therapy.[6]

Treatment with desferrioxamine may also increase susceptibility to mucormycosis. Infections have occurred both in patients with iron overload disorders[7,8] and in those who do not have excessive iron stores.[9-11] A review[8] of 26 cases of mucormycosis in patients undergoing treatment revealed that 23 patients died; in 19 cases the diagnosis was only made at necropsy and only 9 patients received potentially effective treatment (surgery and/or amphotericin B). The organisms responsible were *Rhizopus* species in 13 cases and *Cunninghamella bertholletiae* in 3. In another review of 24 cases of mucormycosis in patients on dialysis,[12] at least 21 were receiving desferrioxamine; infection was fatal in 21 of the 24 patients.

In view of the serious nature of these infections it is important that they should be recognised and treated promptly. It has been suggested that a short course of a suitable antibacterial could be given as prophylaxis to young children from areas with a high incidence of yersiniosis who require treatment with desferrioxamine.[13]

1. Melby K, *et al.* Septicaemia due to Yersinia enterocolitica after oral overdoses of iron. *BMJ* 1982; **285:** 467–8.
2. Scharnetzky M, *et al.* Prophylaxis of systemic yersinosis in thalassaemia major. *Lancet* 1984; **i:** 791.
3. Chiu HY, *et al.* Infection with Yersinia enterocolitica in patients with iron overload. *BMJ* 1986; **292:** 97.
4. Kelly D, *et al.* Yersinia and iron overload. *BMJ* 1986; **292:** 413.
5. Gallant T, *et al.* Yersinia sepsis in patients with iron overload treated with deferoxamine. *N Engl J Med* 1986; **314:** 1643.
6. Gordts B, *et al.* Yersinia pseudotuberculosis septicaemia in thalassaemia major. *Lancet* 1984; **i:** 41–2.
7. Sane A, *et al.* Deferoxamine treatment as a risk factor for zygomycete infection. *J Infect Dis* 1989; **159:** 151–2.
8. Daly AL, *et al.* Mucormycosis: association with deferoxamine therapy. *Am J Med* 1989; **87:** 468–71.
9. Goodill JJ, Abuelo JG. Mucormycosis–a new risk of deferoxamine therapy in dialysis patients with aluminum or iron overload? *N Engl J Med* 1987; **316:** 54.
10. Windus DW, *et al.* Fatal rhizopus infections in hemodialysis patients receiving deferoxamine. *Ann Intern Med* 1987; **107:** 678–80.
11. Boelaert JR, *et al.* Mucormycosis infections in dialysis patients. *Ann Intern Med* 1987; **107:** 782–3.
12. Boelaert JR, *et al.* Mucormycosis among patients on dialysis. *N Engl J Med* 1989; **321:** 190–1.
13. Hadjiminas JM. Yersiniosis in acutely iron-loaded children treated with desferrioxamine. *J Antimicrob Chemother* 1988; **21:** 680–1.

Pregnancy. Desferrioxamine has been associated with fetal abnormalities in *animals*, and is generally only recommended in pregnancy if the benefits are considered to outweigh the risks. A review[1] of pregnancy outcome following iron overdose found that of 66 patients reported to the UK Teratology Information Service, 35 of whom had received desferrioxamine, 7 gave birth to infants with malformations (severe in one). However, in each case overdosage had occurred after the first trimester and the malformations therefore could not be directly related to either iron or desferrioxamine. It was concluded that treatment of iron overdose with desferrioxamine should not be withheld solely on the grounds of pregnancy. Long-term use of desferrioxamine has also been reported in pregnant patients with thalassaemia; a case report[2] and review of the literature found no evidence of teratogenicity despite use at various stages of gestation, suggesting that desferrioxamine may be given to the mother if necessary.

1. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; **12:** 579.
2. Singer ST, Vichinsky EP. Deferoxamine treatment during pregnancy: is it harmful? *Am J Hematol* 1999; **60:** 24–6.

Interactions

Desferrioxamine is usually given parenterally and thus drug interactions due to chelation with oral metal ions are not a problem.

Ascorbic acid. Ascorbic acid is often given in addition to desferrioxamine to patients with iron overload to achieve better iron excretion. However, early on in treatment when there is excess tissue iron there is some evidence that ascorbic acid may worsen the iron toxicity, particularly to the heart. Thus, ascorbic acid should not be given for the first month after starting desferrioxamine treatment.

Phenothiazines. Neurological symptoms including loss of consciousness occurred in 2 patients given *prochlorperazine* during desferrioxamine therapy,[1] possibly due to synergistic effects on iron mobilisation. UK licensed product information therefore advises that they should not be used together.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; **56:** 345–55.

Pharmacokinetics

Desferrioxamine mesilate is poorly absorbed from the gastrointestinal tract. After parenteral administration, desferrioxamine forms chelates with metal ions, which are then excreted in the urine; it is also metabolised,

primarily in the plasma. The iron-desferrioxamine chelate is excreted in the urine and bile. Desferrioxamine is absorbed during peritoneal dialysis if added to the dialysis fluid. It is also removed by dialysis.

◊ References.

1. Summers MR, *et al.* Studies in desferrioxamine and ferrioxamine metabolism in normal and iron-loaded subjects. *Br J Haematol* 1979; **42:** 547–55.
2. Allain P, *et al.* Pharmacokinetics and renal elimination of desferrioxamine and ferrioxamine in healthy subjects and patients with haemochromatosis. *Br J Clin Pharmacol* 1987; **24:** 207–12.
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Uses and Administration

Desferrioxamine is a chelator that has a high affinity for ferric iron. When given by injection it forms a stable water-soluble iron-complex (ferrioxamine) that is readily excreted in the urine and in bile. Desferrioxamine appears to remove both free iron and bound iron from haemosiderin and ferritin but not from haemoglobin, transferrin, or cytochromes. It is estimated that 100 mg of desferrioxamine mesilate could bind about 8.5 mg of iron but it is unlikely that such a figure could be achieved in practice. Desferrioxamine also has an affinity for other trivalent metal ions including aluminium and theoretically 100 mg of the mesilate could bind 4.1 mg of aluminium.

Desferrioxamine increases the excretion of iron from the body and is used in conditions associated with chronic iron overload (such as the iron storage disorders haemochromatosis and haemosiderosis and after repeated blood transfusions as in thalassaemia) and in acute iron poisoning. It has been used as eye drops in the management of ocular siderosis and corneal rust stains. It is also used to reduce aluminium overload in patients with end-stage renal failure on maintenance dialysis.

Desferrioxamine is used as the mesilate and may be given by subcutaneous or intravenous infusion, by intramuscular injection, or intraperitoneally. It has been given orally in acute iron poisoning but this is no longer generally recommended (see Iron Poisoning, below).

In the treatment of **chronic iron overload**, the dosage and route of administration should be determined for each patient by monitoring urinary iron excretion, with the aim of normalising serum-ferritin concentrations. Continuous subcutaneous infusions, preferably with the aid of a small portable infusion pump, are particularly convenient for ambulant patients and are more effective than intramuscular injections. Continuous intravenous infusion has been recommended for patients incapable of continuing subcutaneous infusions or for those with cardiac problems secondary to iron overload. An initial daily dose of desferrioxamine mesilate 500 mg may be given by subcutaneous infusion or intravenous infusion, increasing until a plateau of iron excretion is reached. The usual effective dose range is 20 to 60 mg/kg daily. Subcutaneous infusions are given 3 to 7 times a week depending on the degree of iron overload, usually over 8 to 12 hours, but infusion over 24 hours may be necessary in some patients. For intramuscular injection, an initial dose of 0.5 to 1 g daily as 1 or 2 injections has been used, with the maintenance dose determined by response. It has been suggested that in addition to intramuscular treatment, up to 2 g of desferrioxamine mesilate should be given by intravenous infusion for each unit of blood transfused, at a rate not more than 15 mg/kg per hour at the time of each blood transfusion. Desferrioxamine should be given separately from the blood. Ascorbic acid supplements can enhance the excretion of iron, but, to reduce the risk of toxicity, should not be started until 1 month after starting desferrioxamine treatment (see under Interactions, above). Ascorbic acid is given in doses of up to 200 mg daily for adults or 50 to 200 mg daily for children; it also enhances iron absorption and should therefore be given separately from food.

Desferrioxamine has been used as a *diagnostic test* for iron storage disease in patients with normal renal function by injecting 500 mg of the mesilate intramuscularly and estimating the excretion of iron in the urine collected over the next 6 hours; an excretion of more than 1 mg of iron is suggestive of iron storage disease and more than 1.5 mg can be regarded as pathological.

In the treatment of **acute iron poisoning**, desferrioxamine is usually given by intravenous infusion, particularly in patients who are symptomatic. However, US licensed product information advises intramuscular injection unless the patient is in shock, due to the risk of adverse effects with the intravenous route. The dose should be adjusted according to the severity of the poisoning, preferably as indicated by the serum-iron concentration and total iron binding capacity, if available, although chelation therapy should be started in patients with significant symptoms without waiting for the results of blood concentrations. In the UK, the usual initial dose of desferrioxamine mesilate is 15 mg/kg per hour by slow intravenous infusion, reducing after 4 to 6 hours to provide a total dose not exceeding 80 mg/kg in 24 hours, although larger doses may be tolerated. Alternatively, it may be given intramuscularly as a single dose of 2 g for adults or 1 g for children. In the USA, an initial dose of 1 g is given, either intravenously at a maximum rate of 15 mg/kg per hour, or by intramuscular injection; subsequent doses of 500 mg may be given, by infusion over 4 to 12 hours or intramuscularly at intervals of 4 to 12 hours, to a maximum of 6 g in 24 hours.

In the treatment of **aluminium overload** in patients with end-stage renal failure, those undergoing maintenance haemodialysis or haemofiltration may be given desferrioxamine mesilate 5 mg/kg once a week by slow intravenous infusion during the last hour of a dialysis session, or 5 hours before dialysis in patients with more severe overload. In patients on peritoneal dialysis (CAPD or CCPD), desferrioxamine mesilate 5 mg/kg may be given once a week, by slow intravenous infusion, subcutaneously, intramuscularly, or intraperitoneally (the recommended route) before the final exchange of the day. For the *diagnosis* of aluminium overload, desferrioxamine mesilate 5 mg/kg is given by slow intravenous infusion during the last hour of haemodialysis. An increase in serum-aluminium concentration above baseline of more than 150 nanograms/mL (measured at the start of the next dialysis session) suggests aluminium overload.

Eye drops containing desferrioxamine mesilate 10% have been used for the treatment of ocular siderosis and corneal rust stains.

Administration. Compliance may be a problem with standard parenteral desferrioxamine regimens in patients with chronic iron overload. The oral,[1-3] rectal,[4] and intranasal[5] routes have therefore been tried as alternatives, but results have generally been disappointing. Twice-daily subcutaneous bolus injection has also been reported,[6-9] although the volume of the injection may be a limiting factor.[9]

Intraperitoneal desferrioxamine may be used to reduce aluminium levels in patients receiving peritoneal dialysis for chronic renal failure. Good results have also been reported[10] in a patient with haemochromatosis complicated by cirrhosis and cardiomyopathy, in whom a chronic peritoneal dialysis catheter was used to control ascites and to give desferrioxamine.

1. Callender ST, Weatherall DJ. Iron chelation with oral desferrioxamine. *Lancet* 1980; **ii:** 689.
2. Jacobs A, Chang Ting W. Iron chelation with oral desferrioxamine. *Lancet* 1980; **ii:** 794.
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4. Kontoghiorghes G, *et al.* Desferrioxamine suppositories. *Lancet* 1983; **ii:** 454.
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9. Franchini M, *et al.* Safety and efficacy of subcutaneous bolus injection of deferoxamine in adult patients with iron overload: an update. *Blood* 2004; **103:** 747–8.
10. Swartz RD, Legault DJ. Long-term intraperitoneal deferoxamine for hemochromatosis. *Am J Med* 1996; **100:** 308–12.

Aluminium overload. Desferrioxamine is an effective aluminium chelator and may have a role in both acute and chronic aluminium toxicity.

Accumulation of aluminium may be a particular problem in patients with chronic renal failure and has been implicated in renal osteodystrophy and dialysis dementia, as well as in other conditions, see Aluminium p.2254. The main sources in patients with renal failure are aluminium-containing phosphate binders and the use of tap water with a high aluminium content in the preparation of dialysis fluids. Acute aluminium toxicity is less common, but may occur following exposure to soluble aluminium salts.

Use of alternative phosphate binders (see Renal Osteodystrophy, p.1086) and limits on the aluminium concentration of dialysis fluids reduce the exposure to aluminium in patients with chronic renal failure, but desferrioxamine may also be used to remove aluminium that has already accumulated. The desferrioxamine-aluminium chelate (aluminoxamine) is removed by haemoperfusion and by haemodialysis,[1] and also by peritoneal dialysis, although the amount removed may be much less, and desferrioxamine has been used successfully to treat aluminium overload in dialysis patients. It has also been used with dialysis in acute toxicity.

In patients with *dialysis encephalopathy,* increased aluminium excretion and clinical improvement has been reported[2,3] in patients given desferrioxamine in doses of up to 6 g once a week via the arterial line during the first 2 hours of haemodialysis.[2,3] A study[4] of 11 patients with dialysis encephalopathy found that 5 patients who were treated with deionised or reverse-osmosis water alone died, whereas of 6 who were also given desferrioxamine 6 to 10 g intravenously each week at dialysis, 4 showed clinical improvement. Substantial improvement in early aluminium encephalopathy has been achieved in a patient on continuous ambulatory peritoneal dialysis by using intraperitoneal desferrioxamine.[5] Another small study[6] found that desferrioxamine improved psychomotor function in haemodialysis patients with impaired cerebral function but no clinical encephalopathy, who had only mildly elevated plasma-aluminium concentrations; desferrioxamine was given 3 times weekly during dialysis. Improvement in acute encephalopathy related to alum bladder irrigation has also been reported.[7] However, use of desferrioxamine may also exacerbate encephalopathy and caution is required (see Aluminium Encephalopathy, under Precautions, above).

Desferrioxamine has produced rapid clinical improvement in patients with *dialysis-related bone disease.*[8-10] In some studies[9,10] this has been associated with a reduction in the aluminium content of bone; others[8] have reported clinical improvement with no apparent effect on bone aluminium. Diagnosis of aluminium-related bone disease may require bone biopsy, but some studies have suggested that measurement of plasma-aluminium concentrations after a desferrioxamine infusion may also be used. Some studies reporting positive results[9,11] have used relatively high doses of desferrioxamine (40 mg/kg) with plasma-aluminium measured 24 to 44 hours later; a study[10] using a lower dose of desferrioxamine (28.5 mg/kg) and measuring plasma aluminium 5 hours later found similar increases in patients both with and without bone-aluminium accumulation. However, others have reported[12] that lower doses of desferrioxamine (5 or 10 mg/kg) are adequate when combined with measurement of serum-parathyroid hormone concentrations.

Desferrioxamine therapy has also produced beneficial results in *dialysis patients with anaemia*[13-15] and has also been found to reverse aluminium-induced resistance to erythropoietin.[16,17]

Prurigo nodularis in chronic aluminium overload has responded to desferrioxamine, with resolution of itch and skin lesions.[18]

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4. Milne FJ, *et al.* Low aluminium water, desferrioxamine, and dialysis encephalopathy. *Lancet* 1982; **ii:** 502.
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11. Milliner DS, *et al.* Use of deferoxamine infusion test in the diagnosis of aluminium-related osteodystrophy. *Ann Intern Med* 1984; **101:** 775–80.

12. D'Haese PC, *et al.* Use of the low-dose desferrioxamine test to diagnose and differentiate between patients with aluminium-related bone disease, increased risk for aluminium toxicity, or aluminium overload. *Nephrol Dial Transplant* 1995; **10:** 1874–84.
13. de la Serna F-J, *et al.* Improvement in the erythropoiesis of chronic haemodialysis patients with desferrioxamine. *Lancet* 1988; **i:** 1009–11.
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16. Rosenlöf K, *et al.* Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; **335:** 247–9.
17. Zachée P, *et al.* Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; **335:** 1038–9.
18. Brown MA, *et al.* Prurigo nodularis and aluminium overload in maintenance haemodialysis. *Lancet* 1992; **340:** 48.

Iron overload. Chronic iron overload can be caused by inappropriately increased gastrointestinal absorption, by grossly excessive oral intake over long periods, or by parenteral administration of iron, for example from transfused blood.[1,2] Excess iron is stored in the form of ferritin and haemosiderin. The term *haemosiderosis* is applied to the accumulation of haemosiderin in body tissues without associated tissue damage; *haemochromatosis* refers to a chronic disease state in which iron overload leads to tissue damage, mainly in the heart, liver, and pancreas. Primary or hereditary haemochromatosis is caused by a genetic defect in iron metabolism that results in excessive gastrointestinal absorption of iron. The treatment of choice for primary haemochromatosis is phlebotomy,[1-7] but chelation therapy may be needed in patients with anaemia, hypoproteinaemia, or severe cardiac disease. Neonatal haemochromatosis is a rare condition of unknown cause and results in fetal death or severe liver injury. Antioxidants and iron chelators may improve prognosis,[8] but many infants require liver transplantation. Maternal treatment with normal immunoglobulins has also been reported[9] to reduce the severity of recurrent neonatal haemochromatosis. Secondary or acquired haemochromatosis is commonly associated with chronic anaemias, in particular thalassaemia, in which excessive iron uptake due to disordered erythropoiesis and excess iron from repeated blood transfusions contribute to iron overload.[1,2] These patients generally require iron chelation, usually with parenteral desferrioxamine although oral iron chelators such as deferasirox and deferiprone have also been used (see below).

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3. Barton JC, *et al.* Management of hemochromatosis. *Ann Intern Med* 1998; **129:** 932–9.
4. Hall CJ, *et al.* Haemochromatosis: a time for guidelines? *Hosp Med* 1999; **60:** 884–90.
5. Vautier G, *et al.* Hereditary haemochromatosis: detection and management. *Med J Aust* 2001; **175:** 418–21.
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8. Flynn DM, *et al.* Progress in treatment and outcome for children with neonatal haemochromatosis. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F124–F127.
9. Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. *Lancet* 2004; **364:** 1690–8.

THALASSAEMIA. Patients homozygous for β-thalassaemia (p.1045) have severe anaemia requiring regular blood transfusions. As a consequence of this treatment iron overload develops and the excessive deposition of iron in the myocardium usually results in these patients dying in their second or third decade from arrhythmias or cardiac failure. Iron chelators such as desferrioxamine are therefore used to retard the accumulation of iron.

Desferrioxamine has been shown to prevent complications and improve survival in thalassaemic patients given regular systemic therapy.[1-3] There is also some evidence that impaired organ function might improve with intensive therapy. The liver is the main site of iron accumulation in iron overload, and a reduction in liver-iron concentrations and improvement in liver function has been reported[4] in patients with transfusional iron overload treated with desferrioxamine 2 to 4 g by slow subcutaneous infusion over 12 hours on 6 nights a week. However, in another study[5] improvement in the degree of hepatic fibrosis was seen after 3 to 5 years in only 2 of 7 patients given desferrioxamine up to 85 mg/kg daily by subcutaneous injection, despite reductions in iron concentrations. Preservation or possibly improvement in cardiac function has also been reported,[6-8] although cardiac disease continues to be the main cause of death in patients with thalassaemia. Although initial studies used intramuscular treatment, increased iron excretion is seen with continuous subcutaneous infusion, and this is usually the preferred route. However, compliance may be a problem, and is a major determinant of the effectiveness of treatment.[2] Intensive intravenous therapy, using continuous infusion devices, has been used successfully[9] in patients inadequately treated with subcutaneous desferrioxamine, and good results have also been reported[10,11] with intermittent intravenous infusions. Subcutaneous bolus injection has also been used (see Administration, above) although it may not be tolerated in all patients. Better iron excretion may be achieved if patients are given ascorbic acid 100 to 200 mg daily in addition to desferrioxamine (but see under Interactions, above). The most appropriate time to start desferrioxamine is not clear. Beginning chelation therapy before puberty could help to ensure normal sexual development in patients with thalassaemia major.[12] Other studies[1,2] have reported that initiation of therapy before severe iron overload develops, and maintenance of low serum-ferritin concentrations, prevents cardiac disease and improves prognosis, suggesting that chelation therapy should be started as early as possible, to prevent organ damage developing. However, desferrioxamine has been associated with adverse effects on growth (see Effects on Growth Rate, above) and it is usual to delay therapy until children are about 3 years of age, when iron overload becomes significant, although earlier treatment may be required in some cases.[3]

Alternatives to desferrioxamine have also been investigated. Deferiprone, which is given orally, effectively reduces iron overload,[13] but its long-term benefits are controversial. A study[14] in patients with thalassaemia reported progression of hepatic fibrosis in patients given deferiprone, although another study[15] was unable to confirm these findings. Other studies[16,17] have suggested that deferiprone may be superior to desferrioxamine in reducing cardiac complications. A systematic review[18] found no evidence to change treatment recommendations that indicate deferiprone for use in those for whom desferrioxamine is contraindicated or ineffective; the authors acknowledged that there is a need for more research. Good results have been reported[19] with a combination of desferrioxamine and deferiprone, but the safety and efficacy of this regimen remains to be confirmed. Deferasirox, another oral iron chelator, is also used.

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14. Olivieri NF, *et al.* Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998; **339:** 417–23.
15. Wanless IR, *et al.* Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. *Blood* 2002; **100:** 1566–9.
16. Anderson LJ, *et al.* Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. *Lancet* 2002; **360:** 516–20.
17. Piga A, *et al.* Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica* 2003; **88:** 489–96.
18. Roberts DJ, *et al.* Oral deferiprone for iron chelation in people with thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 22/08/07).
19. Wonke B, *et al.* Combined therapy with deferiprone and desferrioxamine. *Br J Haematol* 1998; **103:** 361–4.

Iron poisoning. Despite the frequency of acute poisoning with iron preparations, no universally accepted treatment protocol exists. Diagnosis relies primarily on the history and clinical symptoms, although it is often difficult to determine the amount of iron ingested, and clinical assessment can be misleading since patients may exhibit mild symptoms despite having ingested potentially toxic quantities of iron. Measurement of the serum-iron concentration is useful in assessing the severity of poisoning but may not be immediately available, and does not always correlate with the severity of symptoms. Measurement of total iron binding capacity (TIBC) has been used but may be misleading and is no longer recommended.

Other tests that have been used include the desferrioxamine challenge test, in which desferrioxamine 50 mg/kg (to a maximum dose of 1 g) is given intramuscularly; if free iron is present, ferrioxamine will be excreted in the urine imparting a classic 'vin rosé' colour. However, interpretation is difficult and a negative result does not rule out toxicity; the test is no longer generally recommended.

The initial stage of treatment involves intravenous fluids and other supportive care as appropriate, and this may be sufficient in mild poisoning. Gastric lavage may be performed to remove any unabsorbed iron from the gastrointestinal tract, but may not remove tablets effectively; whole-bowel irrigation is an alternative, particularly in patients suspected of ingesting modified-release preparations or those with radiographic evidence of unabsorbed tablets remaining after gastric lavage. Addition of desferrioxamine to the lavage fluid has been suggested but there is little evidence of efficacy and some concern over possible toxic effects of ferrioxamine, and it is not routinely recommended. Activated charcoal is not effective in iron poisoning.

Chelation therapy with desferrioxamine is indicated in severe poisoning, including patients with impaired consciousness, shock, hypotension, or severe acidosis; other signs of severe poisoning include leucocytosis. A serum-iron concentration above 5 micrograms/mL indicates severe poisoning, and is usually an indication for chelation, but patients with shock or coma should be treated without waiting for the results of serum-iron tests; patients with moderate poisoning (serum-iron concentration 3 to 5 micrograms/mL) may be given chelation therapy if they are symptomatic. There is no general agreement on the duration of chelation therapy; among the suggested end-points are the resolution of severe symptoms, disappearance of the vin rosé coloration of the urine, 24 hours after the disappearance of coloration, and reduction of serum-iron concentrations to the normal range.

General references.

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4. Fine JS. Iron poisoning. *Curr Probl Pediatr* 2000; **30:** 71–90.

Malaria. Following the suggestion that iron-deficiency anaemia may offer some protection against infections (see Infections in the Precautions for Iron, p.1950), desferrioxamine was tried in a few patients with malaria.[1,2] Any antimalarial effect of desferrioxamine was thought to be as a result of chelation of parasite-associated iron rather than reduction in body-iron concentrations in the patient. Desferrioxamine given intravenously was reported[3] to shorten the time to regain consciousness in children with cerebral malaria receiving standard therapy with intravenous quinine and oral pyrimethamine-sulfadoxine. However, in another study[4] there was no evidence of a beneficial effect on mortality when desferrioxamine was added to an antimalarial treatment regimen that included a loading dose of quinine.

1. Gordeuk VR, *et al.* Iron chelation as a chemotherapeutic strategy for falciparum malaria. *Am J Trop Med Hyg* 1993; **48:** 193–7.
2. Thompson DF. Deferoxamine treatment of malaria. *Ann Pharmacother* 1994; **28:** 602–3.
3. Gordeuk V, *et al.* Effect of iron chelation therapy on recovery from deep coma, in children with cerebral malaria. *N Engl J Med* 1992; **327:** 1473–7.
4. Thuma PE, *et al.* Effect of iron chelation therapy on mortality in Zambian children with cerebral malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 214–18.

Porphyria. The management of various forms of porphyria is discussed on p.1448. Desferrioxamine has been used to reduce serum-iron concentrations in porphyria cutanea tarda and may have a role if phlebotomy is contra-indicated. In a study of 25 patients with porphyria cutanea tarda,[1] subcutaneous infusion of desferrioxamine was found to be as effective as repeated phlebotomies in normalising porphyrin excretion and iron storage. Desferrioxamine was also used successfully to treat haemodialysis-related porphyria cutanea tarda in a 22-year-old man in whom venesection therapy was contra-indicated because of severe anaemia requiring multiple blood transfusion.[2] Each course of intravenous desferrioxamine therapy after the end of 3 haemodialysis sessions was accompanied by a marked decrease in plasma porphyrins, a sharp increase in haematocrit values, and a simultaneous improvement in skin lesions.

1. Rocchi E, *et al.* Iron removal therapy in porphyria cutanea tarda: phlebotomy versus slow subcutaneous desferrioxamine infusion. *Br J Dermatol* 1986; **114:** 621–9.
2. Praga M, *et al.* Treatment of hemodialysis-related porphyria cutanea tarda with deferoxamine. *N Engl J Med* 1987; **316:** 547–8.

Preparations

BP 2008: Desferrioxamine Injection;
USP 31: Deferoxamine Mesylate for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Desferal; ***Austral.:*** Desferal; ***Austria:*** Desferal; ***Belg.:*** Desferal; ***Braz.:*** Desferal; ***Canad.:*** Desferal; ***Chile:*** Desferal; ***Cz.:*** Desferal; ***Denm.:*** Desferal; ***Fin.:*** Desferal; ***Fr.:*** Desferal; ***Ger.:*** Desferal; ***Gr.:*** Desferal; ***Hong Kong:*** Desferal; ***Hung.:*** Desferal; ***India:*** Desferal; ***Indon.:*** Desferal; ***Irl.:*** Desferal; ***Israel:*** Desferal; ***Ital.:*** Desferal; ***Malaysia:*** Desferal; ***Mex.:*** Desferal; ***Neth.:*** Desferal; ***Norw.:*** Desferal; ***NZ:*** Desferal†; ***Pol.:*** Desferal; ***Port.:*** Desferal; ***Rus.:*** Desferal (Десферал); ***S.Afr.:*** Desferal; ***Spain:*** Des-

ferin; ***Swed.:*** Desferal; ***Switz.:*** Desferal; ***Thai.:*** Desferal; ***Turk.:*** Desferal; ***UK:*** Desferal; ***USA:*** Desferal; ***Venez.:*** Desferal.

Dexrazoxane *(BAN, USAN, rINN)*

ADR-529; Dexrazoxano; Dexrazoxanum; ICRF-187; NSC-169780. (+)-(*S*)-4,4′-Propylenebis(piperazine-2,6-dione).

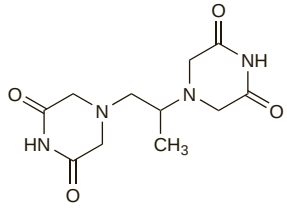
Декразоксан

$C_{11}H_{16}N_4O_4$ = 268.3.

CAS — 24584-09-6.

ATC — V03AF02.

ATC Vet — QV03AF02.



Adverse Effects and Precautions

Dexrazoxane may add to the bone-marrow depression caused by antineoplastics and frequent complete blood counts are recommended during therapy. Although dexrazoxane protects against the cardiotoxic effects of anthracyclines, cardiac function should continue to be monitored when dexrazoxane is used. Pain on injection has been reported.

When used to reduce the cardiotoxicity of doxorubicin, licensed product information in the USA recommends that dexrazoxane should only be given to patients who have received a cumulative dose of doxorubicin of 300 mg/m^2 and who require continued use, since there is some evidence that dexrazoxane may reduce the efficacy of some antineoplastic regimens.

Patients with known liver function disorders should have their liver function assessed before receiving dexrazoxane for anthracycline extravasation.

Effects on the skin. Severe cutaneous and subcutaneous necrosis has been reported[1] in a patient who received dexrazoxane by infusion into a peripheral forearm vein, followed by intravenous injection of doxorubicin at a different site in the same arm. Local pain occurred during the dexrazoxane infusion but there was no evidence of extravasation.

1. Lossos IS, Ben-Yehuda D. Cutaneous and subcutaneous necrosis following dexrazoxane-CHOP therapy. *Ann Pharmacother* 1999; **33:** 253–4.

Pharmacokinetics

Dexrazoxane is mainly excreted in the urine as unchanged drug and metabolites. The elimination half-life is reported to be about 2 hours.

Uses and Administration

Dexrazoxane is the (+)-enantiomorph of the antineoplastic drug razoxane (p.767) and is a cytoprotective agent that is used to reduce the cardiotoxicity of doxorubicin and other anthracyclines (see p.713); it is also used in the management of anthracycline extravasation. It is hydrolysed to an active metabolite that is similar to edetic acid. This chelates iron within the cells and appears to prevent the formation of the anthracycline-iron complex that is thought to be responsible for cardiotoxicity.

Dexrazoxane is used to reduce the incidence and severity of cardiomyopathy associated with doxorubicin or epirubicin in patients with advanced or metastatic cancer who have previously received anthracyclines; in the USA, it is only licensed for use in women with metastatic breast cancer who have received a cumulative dose of doxorubicin of 300 mg/m^2 and who require continued use. It is given as the hydrochloride, by slow intravenous injection or rapid intravenous infusion, starting within 30 minutes before the anthracycline. The dose is expressed as the base. In the USA, the dose is calculated on a 10:1 ratio with doxorubicin; typically, 500 mg/m^2 of dexrazoxane is given for every 50 mg/m^2 of doxorubicin. In the UK the dose is calculated on a 20:1 ratio with doxorubicin and a 10:1 ratio with epirubicin. A reduction in dose may be required in patients with renal impairment (see below).

In patients with anthracycline extravasation, dexrazoxane is given intravenously into a large vein in an area other than that affected by the extravasation. It is given once daily for 3 days, by intravenous infusion over 1 to 2 hours, starting within 6 hours of extravasation; the dose should be given at about the same time each day. The usual dose is 1000 mg/m^2 on the first and second days, and 500 mg/m^2 on the third day; the maximum single dose for patients with a body-surface greater than 2 m^2 is 2000 mg.

Dexrazoxane is also being investigated for use in various other malignancies.

◊ References.

1. Links M, Lewis C. Chemoprotectants: a review of their clinical pharmacology and therapeutic efficacy. *Drugs* 1999; **57:** 293–308.
2. Schuchter LM, *et al.* 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2002; **20:** 2895–903. Also available at: http://www.jco.org/cgi/reprint/20/12/2895.pdf (accessed 04/10/05)
3. Cvetković RS, Scott LJ. Dexrazoxane : a review of its use for cardioprotection during anthracycline chemotherapy. *Drugs* 2005; **65:** 1005–24.

Administration in children. Doxorubicin has been used in the treatment of acute lymphoblastic leukaemia in children but cardiotoxicity may be a problem. A randomised study[1] in 206 children found that those given dexrazoxane with doxorubicin had fewer elevations of cardiac troponin T, a marker of myocardial damage, than those given doxorubicin alone, but longer follow-up was needed to assess effects on cardiac function and survival. Another study[2] in children with Hodgkin's disease suggested that use of dexrazoxane might increase the risk of secondary malignancies, but further analysis of the leukaemia study[3] found no evidence of such an effect.

1. Lipshultz SE, *et al.* The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 2004; **351:** 145–53.
2. Tebbi CK, *et al.* Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol* 2007; **25:** 493–500.
3. Barry EV, *et al.* Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *J Clin Oncol* 2008; **26:** 1106–11.

Administration in renal impairment. Dexrazoxane is mainly excreted in the urine and the dose should be reduced in patients with renal impairment. A reduction of 50% is recommended for patients with a creatinine clearance below 40 mL/minute.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Cardioxane; ***Braz.:*** Cardioxane; ***Canad.:*** Zinecard; ***Cz.:*** Cardioxane; Savene; ***Denm.:*** Cardioxane; ***Fr.:*** Cardioxane; ***Gr.:*** Savene; ***Hung.:*** Cardioxane; ***Irl.:*** Cardioxane; ***Israel:*** Cardioxane; ***Ital.:*** Cardioxane; ***Mex.:*** Cardioxane; ***Pol.:*** Cardioxane; ***UK:*** Cardioxane; Savene; ***USA:*** Totect; Zinecard; ***Venez.:*** Cardioxane.

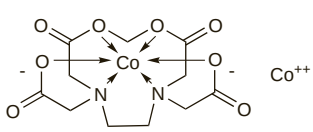
Dicobalt Edetate *(BAN, rINN)*

Cobalt Edetate; Cobalt EDTA; Cobalt Tetracemate; Dicobalti Edetas; Dikobalt Edetat; Édétate Dicobaltique; Edetato de dicobalto; Edetato dicobaltio. Cobalt [ethylenediaminetetra-acetato(4–)-*N,N′,O,O′*]cobalt(II).

Дикобальта Эдетат

$C_{10}H_{12}Co_2N_2O_8$ = 406.1.

CAS — 36499-65-7.



Adverse Effects and Precautions

Dicobalt edetate may cause hypotension, tachycardia, and vomiting. Anaphylactic reactions have occurred; oedema of the face and neck, sweating, chest pain, cardiac irregularities, and skin rashes have been reported.

The adverse effects of dicobalt edetate are more severe in the absence of cyanide. Therefore, dicobalt edetate should not be given unless cyanide poisoning is definitely confirmed and poisoning is moderate or severe, that is, when consciousness is impaired.

Oedema. A patient with cyanide toxicity developed severe facial and pulmonary oedema after treatment with dicobalt edetate.[1] It has been suggested that when dicobalt edetate is used, facilities for intubation and resuscitation should be immediately available.

1. Dodds C, McKnight C. Cyanide toxicity after immersion and the hazards of dicobalt edetate. *BMJ* 1985; **291:** 785–6.

Uses and Administration

Dicobalt edetate is a chelator used in the treatment of acute cyanide poisoning (p.2045). Its use arises from the property of cobalt salts to form a relatively non-toxic stable ion-complex with cyanide. Owing to its toxicity, dicobalt edetate should be used only in confirmed cyanide poisoning and never as a precautionary measure. Cyanide poisoning must be treated as quickly as possible. A suggested dose is 300 mg given by intravenous injection over about 1 minute, repeated if the response is inadequate; a further dose of 300 mg of dicobalt edetate may be given 5 minutes later if required. For less severe poisoning the injection should be given over 5 minutes. Each injection of dicobalt edetate may be followed immediately by 50 mL of glucose 50% intravenously to reduce toxicity, though the value of giving glucose has been questioned.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Kelocyanor; ***Gr.:*** Kelocyanor.

Digoxin-specific Antibody Fragments

Digoxin Immune Fab (Ovine); F(ab); Fragmentos de anticuerpos específicos antidigoxina.

ATC — V03AB24.

ATC Vet — QV03AB24.

Adverse Effects and Precautions

Allergic reactions to digoxin-specific antibody fragments have been reported rarely. Patients known to be allergic to sheep protein and patients who have previously received digoxin-specific antibody fragments are likely to be at greater risk of developing an allergic reaction. Blood pressure, ECG, and potassium concentrations should be monitored closely during and after use.

Uses and Administration

Digoxin-specific antibody fragments are derived from antibodies produced in sheep immunised to digoxin. Digoxin has greater affinity for the antibodies than for tissue-binding sites, and the digoxin-antibody complex is then excreted in the urine. Digoxin-specific antibody fragments are generally restricted to the treatment of life-threatening digoxin or digitoxin intoxication in which conventional treatment is ineffective. Successful treatment of lanatoside C poisoning has also been reported.

It is estimated that 38 mg of antibody fragments could bind about 500 micrograms of digoxin or digitoxin and the dose calculation is based on this estimate and the body-load of digoxin (based on the amount ingested or ideally from the steady-state plasma concentration). Administration is by intravenous infusion over a 30-minute period. If cardiac arrest is imminent the dose may be given as a bolus. In the case of incomplete reversal or recurrence of toxicity a further dose can be given. In patients considered to be at high risk of an allergic response an intradermal or skin scratch test may be performed.

◊ Clinical studies[1-3] and reviews[4] of the use of digoxin-specific antibody fragments have confirmed their effectiveness in the treatment of severe digitalis toxicity in the majority of patients. An initial response is usually seen within 30 minutes of the end of the infusion with a maximum response after 3 to 4 hours.[4] The main causes of treatment failure or partial response are incorrect