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).

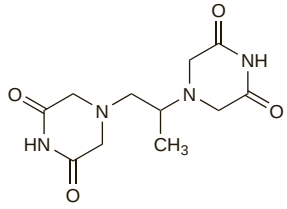
Декразоксан

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

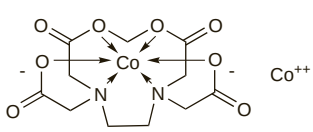
Dicobalt Edetate *(BAN, rINN)*

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

diagnosis of digitalis intoxication, inadequate dosage of antibody fragments, and use in patients already moribund.[3,4] Few adverse reactions have been attributed to the use of digoxin-specific antibody fragments; a few cases of minor allergic reactions have been reported including erythema, facial swelling, urticaria, and rashes,[2,4] but no anaphylactic reactions have been reported.[1-4] Haemodynamic status normally improves, but withdrawal of the inotropic support provided by digoxin may produce a decline in cardiac function in some patients. There may be dramatic reductions in plasma potassium concentrations.

Treatment has been successful in patients with varying degrees of renal impairment.[2,4,5] Elimination of the antibody fragment-digoxin complex may be markedly delayed in severe renal impairment and prolonged monitoring may be required in such patients.[6] Measurement of free serum-digoxin concentrations may be useful.[7] Experience with digoxin-specific antibody fragments in a patient with chronic renal failure receiving haemodialysis has been reported.[8] The patient had a good clinical response but haemodialysis did not remove the antibody fragment-digoxin complex.

In patients with adequate renal function the half-life of the antibody fragment-digoxin complex has been reported[2] to be about 16 to 20 hours although longer half-lives have been reported.[9] It has been suggested[10] that giving digoxin-specific antibody fragments by infusion over 7 hours, after an initial loading dose, could be useful in ensuring adequate antibody concentrations are maintained to bind digoxin as it is released from tissue stores over a prolonged period.

Use of the antibody fragments has also been effective in children with severe digitalis intoxication.[11]

Digoxin-specific antibody fragments have also been used successfully in poisoning due to preparations containing toad venom,[12] or due to common or yellow oleander (see Oleander, p.2356).

1. Smith TW, *et al.* Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: experience in 26 cases. *N Engl J Med* 1982; **307:** 1357–62.
2. Wenger TL, *et al.* Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. *J Am Coll Cardiol* 1985; **5:** 118A–123A.
3. Antman EM, *et al.* Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: final report of a multicenter study. *Circulation* 1990; **81:** 1744–52.
4. Flanagan RJ, Jones AL. Fab antibody fragments: some applications in clinical toxicology. *Drug Safety* 2004; **27:** 1115–33.
5. Allen NM, *et al.* Clinical and pharmacokinetic profiles of digoxin immune Fab in four patients with renal impairment. *DICP Ann Pharmacother* 1991; **25:** 1315–20.
6. Ujhelyi MR, *et al.* Disposition of digoxin immune Fab in patients with kidney failure. *Clin Pharmacol Ther* 1993; **54:** 388–94.
7. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; **28:** 483–93.
8. Clifton GD, *et al.* Free and total serum digoxin concentrations in a renal failure patient after treatment with digoxin immune Fab. *Clin Pharm* 1989; **8:** 441–5.
9. Gibb I, Parnham A. A star treatment for digoxin overdose? *BMJ* 1986; **293:** 1171–2.
10. Schaumann W, *et al.* Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986; **30:** 527–33.
11. Woolf AD, *et al.* The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med* 1992; **326:** 1739–44.
12. Brubacher JR, *et al.* Treatment of toad venom poisoning with digoxin-specific Fab fragments. *Chest* 1996; **110:** 1282–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Digibind; ***Austria:*** Digitalis Antidot†; ***Belg.:*** Digitalis Antidot; ***Canad.:*** Digibind; ***Fr.:*** Digidot†; ***Ger.:*** Digitalis Antidot; ***Gr.:*** Digibind†; DigiFab; ***Hong Kong:*** Digitalis Antidote; ***Swed.:*** Digitalis Antidot; ***Switz.:*** Digitalis Antidot; ***UK:*** Digibind; ***USA:*** Digibind; DigiFab.

Dimercaprol *(BAN, rINN)*

BAL; British Anti-Lewisite; Dimercaprolum; Dimerkaprol; Dimerkaproli; Dimerkaprolis. 2,3-Dimercaptopropan-1-ol.

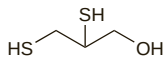
Димеркапрол

$C_3H_8OS_2$ = 124.2.

CAS — 59-52-9.

ATC — V03AB09.

ATC Vet — QV03AB09.



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

Ph. Eur. 6.2 (Dimercaprol). A clear colourless or slightly yellow liquid. Soluble in water and in arachis oil; miscible with alcohol and with benzyl benzoate. Store at 2° to 8° in well-filled airtight containers. Protect from light.

USP 31 (Dimercaprol). A colourless or practically colourless liquid, having a disagreeable, mercaptan-like odour. Soluble 1 in 20 of water; soluble in alcohol, in benzyl benzoate, and in methyl alcohol. Store at a temperature not exceeding 8° in airtight containers. Protect from light.

Adverse Effects and Treatment

The most consistent adverse effects produced by dimercaprol are hypertension and tachycardia. Other adverse effects include nausea, vomiting, headache, burning sensation of the lips, mouth, throat, and eyes, lachrymation and salivation, tingling of the extremities, a sensation of constriction in the throat and chest, muscle pains and muscle spasm, rhinorrhoea, conjunctivitis, sweating, restlessness, and abdominal pain. Transient reductions in the leucocyte count have also been reported. Pain may occur at the injection site and sterile abscesses occasionally develop. In children, fever commonly occurs and persists during therapy.

Adverse effects are dose-related, relatively frequent, and usually reversible. It has been suggested that ephedrine sulfate 30 to 60 mg, given by mouth 30 minutes before each injection of dimercaprol, may reduce adverse effects; antihistamines may alleviate some of the symptoms.

Precautions

Dimercaprol should be used with care in patients with hypertension or renal impairment. It should be discontinued, or continued with extreme caution, if acute renal insufficiency develops during therapy. Alkalinisation of the urine may protect the kidney during therapy by stabilising the dimercaprol-metal complex. Dimercaprol should not be used in patients with hepatic impairment unless due to arsenic poisoning. It should not be used in the treatment of poisoning due to cadmium, iron, or selenium as the dimercaprol-metal complexes formed are more toxic than the metals themselves.

G6PD deficiency. Haemolysis has been reported[1] during chelation therapy with dimercaprol and sodium calcium edetate for high blood-lead concentrations in 2 children with a deficiency of G6PD.

1. Janakiraman N, *et al.* Hemolysis during BAL chelation therapy for high blood lead levels in two G6PD deficient children. *Clin Pediatr (Phila)* 1978; **17:** 485–7.

Interactions

Iron supplements should not be given during dimercaprol therapy as toxic dimercaprol-metal complexes are formed.

Pharmacokinetics

After intramuscular injection, maximum blood concentrations of dimercaprol may be attained within 30 to 60 minutes. Dimercaprol is rapidly metabolised and the metabolites and dimercaprol-metal chelates are excreted in the urine and bile. Elimination is essentially complete within 4 hours of a single dose.

Uses and Administration

Dimercaprol is a chelator used in the treatment of acute poisoning by arsenic (p.2261), gold (p.123), and mercury (p.2342); it may also be used in the treatment of poisoning by antimony, bismuth, and possibly thallium. It is also used, with sodium calcium edetate, in acute lead poisoning (p.2332).

The sulfhydryl groups on dimercaprol compete with endogenous sulfhydryl groups on proteins such as enzymes to combine with these metals; chelation by dimercaprol therefore prevents or reverses any inhibition of the sulfhydryl enzymes by the metal and the dimercaprol-metal complex formed is readily excreted by the kidney. Since the complex may dissociate, particularly at acid pH, or be oxidised, the aim of treatment is to provide an excess of dimercaprol in body fluids until the excretion of the metal is complete.

Dimercaprol should be given by deep intramuscular injection and the injections should be given at different sites. The usual initial dose is up to 18 mg/kg daily in divided doses on the first day, reducing the daily dose and the frequency of injections over the subsequent days; a minimum interval of 4 hours between doses appears to reduce adverse effects. The individual dose is determined by severity of symptoms and the causative agent. Single doses should not generally exceed 3 mg/kg but single doses of up to 5 mg/kg may be required initially in patients with severe acute poisoning. Various dosage schedules are in use.

In the UK, adults may be given doses of 400 to 800 mg on the first day of treatment, 200 to 400 mg on the second and third days, and 100 to 200 mg on the fourth and subsequent days, all in divided doses; children may be given a similar dose per kg as for adults. Alternatively, the *BNF* recommends a dose for both adults and children of 2.5 to 3 mg/kg every 4 hours for 2 days, 2 to 4 times daily on the third day, then 1 to 2 times daily for 10 days or until recovery.

In the USA, a recommended schedule for severe arsenical or gold poisoning is 3 mg/kg given at 4-hourly intervals throughout the first 2 days, 4 times on the third day, and twice on each of the next 10 days. In milder cases, 2.5 mg/kg is given 4 times daily on each of the first 2 days, twice daily on the third day, and once daily on subsequent days for 10 days or until recovery.

Dimercaprol is also used with sodium calcium edetate (p.1462) in the treatment of lead poisoning and can be of particular value in the treatment of acute lead encephalopathy. Dimercaprol is usually started first, since sodium calcium edetate may cause lead to shift into the CNS. A suggested procedure is to give dimercaprol intramuscularly in an initial dose of 4 mg/kg, followed at 4-hourly intervals by dimercaprol 3 to 4 mg/kg intramuscularly and sodium calcium edetate; the sodium calcium edetate may be given either intravenously, or intramuscularly at a different site from the dimercaprol. Treatment may be continued for 2 to 7 days depending on the clinical response.

Preparations

BP 2008: Dimercaprol Injection;
USP 31: Dimercaprol Injection.

Proprietary Preparations (details are given in Part 3)
Rus.: Zorex (Зорекс).

4-Dimethylaminophenol Hydrochloride

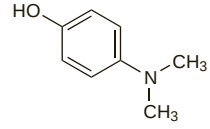
Dimetamfenol Hydrochloride; 4-Dimetilaminofenol, hidrocloruro de; 4-DMAP.

$C_8H_{11}NO,HCl$ = 173.6.

CAS — 619-60-3 (4-dimethylaminophenol); 5882-48-4 (4-dimethylaminophenol hydrochloride).

ATC — V03AB27.

ATC Vet — QV03AB27.



(4-dimethylaminophenol)

Profile

4-Dimethylaminophenol hydrochloride is reported to oxidise haemoglobin to methaemoglobin and has been used with sodium thiosulfate as an alternative to sodium nitrite (p.1464) in the treatment of cyanide poisoning. Doses of 3 to 4 mg/kg have been given intravenously.

◊ References.

1. Weger NP. Treatment of cyanide poisoning with 4-dimethylaminophenol (DMAP)–experimental and clinical overview. *Fundam Appl Toxicol* 1983; **3:** 387–96.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: 4-DMAP; ***Neth.:*** 4-DMAP.