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).

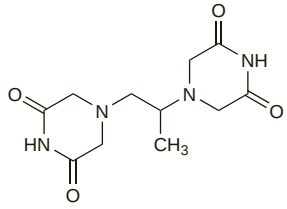
Декразоксан

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

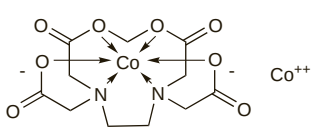
Dicobalt Edetate *(BAN, rINN)*

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