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.

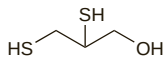
Димеркапрол

$C_3H_8OS_2$ = 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

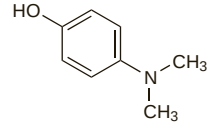
Dimetamfenol Hydrochloride; 4-Dimetilaminofenol, hidrocloruro de; 4-DMAP.

$C_8H_{11}NO,HCl$ = 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.