weight heparin, in addition to aspirin, has therefore also been recommended.[3]

1. Royal College of Obstetricians and Gynaecologists. Thromboembolic disease in pregnancy and the puerperium: acute management (February 2007). Available at: http://www.rcog.org.uk/resources/Public/pdf/green_top_28_thromboembolic_minorrevision.pdf (accessed 05/02/08)
2. Royal College of Obstetricians and Gynaecologists. Thromboprophylaxis during pregnancy, labour and after vaginal delivery (January 2004). Available at: http://www.rcog.org.uk/index.asp?PageID=535 (accessed 23/05/05)
3. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S.
4. Rai R, *et al.* Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997; **314:** 253–7.
5. Empson M, *et al.* Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. *Obstet Gynecol* 2002; **99:** 135–44.

Reperfusion and revascularisation procedures. Heparin has an established role as an adjunct to percutaneous vascular interventions and bypass surgery, to prevent perioperative thrombosis of the target artery, and is usually given with aspirin or other antiplatelet drugs (see Reperfusion and Revascularisation Procedures, p.1181). High doses are used, particularly in patients undergoing bypass surgery with extracorporeal circulation, and bleeding is a common problem. Although heparin may have an antiproliferative effect, treatment with systemic heparin (unfractionated or low-molecular-weight) appears to have no effect on restenosis;[1] however, a study using local application of enoxaparin suggested that restenosis was reduced.[2] Heparin-coated intracoronary stents have also been used; they improve outcomes compared with balloon angioplasty,[3] but have not been shown to be superior to bare-metal stents[4] or to have any additional effect on restenosis.[5,6] Heparin-coated stents have also been used successfully in cerebrovascular interventions.[7]

1. Grassman ED, *et al.* A randomized trial of the low-molecular-weight heparin certoparin to prevent restenosis following coronary angioplasty. *J Invasive Cardiol* 2001; **13:** 723–8.
2. Kiesz RS, *et al.* Local delivery of enoxaparin to decrease restenosis after stenting: results of initial multicenter trial: Polish-American Local Lovenox NIR Assessment study (The POLONIA study). *Circulation* 2001; **103:** 26–31.
3. Serruys PW, *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; **352:** 673–81. Correction. *ibid.*; 1478.
4. Mehran R, *et al.* An Internet-based registry examining the efficacy of heparin coating in patients undergoing coronary stent implantation. *Am Heart J* 2005; **150:** 1171–6.
5. Wöhrle J, *et al.* Comparison of the heparin coated vs the uncoated Jostent —no influence on restenosis or clinical outcome. *Eur Heart J* 2001; **22:** 1808–16.
6. Semiz E, *et al.* Comparison of initial efficacy and long-term follow-up of heparin-coated Jostent with conventional NIR stent. *Jpn Heart J* 2003; **44:** 889–98.
7. Parkinson RJ, *et al.* Use of heparin-coated stents in neurovascular interventional procedures: preliminary experience with 10 patients. *Neurosurgery* 2006; **59:** 812–21.

Preparations

BP 2008: Heparin Injection;
USP 31: Anticoagulant Heparin Solution; Heparin Calcium Injection; Heparin Lock Flush Solution; Heparin Sodium Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Calciparine; Cervep; Croneparina; Parinix†; Riveparin; Serianon; Sobrius; Sodiparin; ***Austral.:*** Calcihep†; Calciparine†; Uniparin†; ***Austria:*** Lipohep; Liquemin; Thrombophob; Thrombophob-S; Venoruton Heparin; Viatromb; ***Belg.:*** Calparine; Liquemine†; ***Braz.:*** Actparin; Alimax; Disotron; Heptar; Liquemine; Parinorth†; Trombofob; ***Canad.:*** Hepalean; Hepalean-Lok; ***Cz.:*** Hepa-Gel†; Hepa-Salbe†; Lioton; Lipohep†; Trombex†; Viatromb; ***Fin.:*** Hepaflex; ***Fr.:*** Calciparine; ***Ger.:*** Calciparin; Essaven 60 000; Exhirud Heparin; Hepa-Gel; Hepa-Salbe; Hepaplus†; Hepathromb; Hepathrombin; Liquemin N; Perivar Venensalbe†; Sportino; Thrombareduct; Thrombophob; Traumalitan†; Venalitan; Venoruton Emulgel; Vetren; ***Gr.:*** Calciparine; Croneparina†; Hep Lok†; Hepsal; Monoparin; Multiparin; Pump-Hep†; ***Hong Kong:*** Lioton; ***Hung.:*** Heparibene; Lioton; ***India:*** Beparine; Thrombophob; ***Indon.:*** Inviclot; Thrombophob; ***Irl.:*** Calciparine†; Hep-Rinse†; Heplok†; Hepsal; Minihep†; Monoparin; Multiparin; Unihep†; ***Israel:*** Calciparin; ***Ital.:*** Ateroclar; Bioclarit†; Calciparina; Clarisco; Croneparina; Disebrin; Ecabil; Ecafast; Ecasolv; Emoklar; Epacalcica; Eparical†; Eparinlider; Eparinovis; Eparven; Epsoclar; Epsodil†; Epsodilave; Eudipar†; Flusolv; Hemofluss†; Isoclar; Lioton; Liquemin†; Mica; Normoparin; Pharepa; Reoflus; Sosefluss; Trombolisin; Zepac; ***Mex.:*** Hep-Tec; Inhepar†; Proparin; ***NZ:*** Monoparin†; Multiparin; ***Pol.:*** Coaparin; Heparizen; Lioton; Lipohep; ***Port.:*** Calciparina†; ***Rus.:*** Lioton (Лиотон); Trombless (Тромблесс); ***S.Afr.:*** Calciparine; Thrombophob; ***Spain:*** Calciparina†; Menaven; ***Switz.:*** Calciparine; Demovarin; Gelparine; HepaGel; Hepasol Lipogel; HepaSpray†; Lioton; Liquemine; ***Turk.:*** Calciparine; Liquemine; Nevparin; ***UK:*** Calciparine†; Canusal; Hepsal; Monoparin; Multiparin; ***USA:*** Hep-Lock; Hepflush; ***Venez.:*** Hirox; Liquemine†; Riveparin.

Multi-ingredient: ***Arg.:*** Contractubex; Venostasin; ***Austria:*** Ambenat; Contractubex; Derivon; Dolo-Menthoneurin; Dolobene; Etrat; Heparin Comp; Ichthalgan forte; Lipactin; Pasta Cool; Pertrombon; Sensicutan; Thrombophob; Venobene; Venostasin compositum; Vetren; ***Belg.:*** Lipactin; ***Braz.:*** Contractubex; Dolobene; Trombofob; Venalot H; Venostasin†; ***Canad.:*** Lipactin; ***Cz.:*** Contractubex; Dolo-Rubriment†; Dolobene; Heparin-Gel†; Sensicutan; ***Fin.:*** Lipactin; Trombosol; ***Fr.:*** Cirkan a la Prednacinolone; Esberiven; ***Ger.:*** Contractubex; Dolo-Menthoneurin†; Dolobene; Enelbin-Salbe N†; Essaven Tri-Complex†; Essaven†; Etrat Sportgel†; Heparin Comp†; Heparin Kombi-Gel†; Heparin Plus†; Ichthalgan†; Kelofibrase†; Lipactin; Ostochont†; Sensicutan; Trauma-Puren†; Venengel†; Venoplant AHS†; ***Hong Kong:*** Contractubex; Dolobene; ***Hung.:*** Contractubex; Dolobene; ***India:*** Beparine; Contractubex; Proctosedyl; Thrombophob; ***Indon.:*** Thrombophob; ***Ital.:*** Edeven; Essaven; Flebs; Idracemi Eparina; Luxazone Eparina; Proctosoll; Reparil; Venotrauma†; Via Mal Traumagel; Vit Eparin; Xantervit Eparina; ***Philipp.:*** Contractubex; ***Pol.:*** Alcepalan; Biherpan; Cepan; Contractubex; Dolobene; Savarix; Tointex; ***Port.:*** DM Gel; ***Rus.:*** Contractubex (Контрактубекс); Dolobene (Долобене); Heparin Ointment (Гепариновая Мазь); Hepatrombin (Гепатромбин); Hepatrombin H (Гепатромбин Г); Nigepan (Нигепан); Venolife (Веналайф); ***S.Afr.:*** Essaven†; ***Spain:*** Essavenon; Venacol; ***Switz.:*** Assan; Assan thermo; Butaparin; Contractubex; Dolo-Arthrosenex; Dolobene; Gorgonium; Hepabuzone; Heparinol; Hepathrombine†; Keli-med; Keppur; Lipactin; Lyman; Phlebostasin compositum†; Ralur†; Sportium; Sportusal; Venoplant comp; Venoplant-N†; Venucreme; Venugel.

Heparinoids

Heparinoides.

Profile

The term heparinoid includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly-sulfated polysaccharides of similar structure. Such compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans; glycosaminoglycan polysulfate compounds; or sulfated mucopolysaccharides.

The following anticoagulants may be described as heparinoids:

- Danaparoid Sodium, p.1255
- Dermatan Sulfate, p.1256
- Pentosan Polysulfate Sodium, p.1367
- Sodium Apolate, p.1397
- Suleparoid, p.1406
- Sulodexide, p.1406

Heparinoid preparations are available with uses ranging from anticoagulation to the alleviation of inflammation (applied topically); some are claimed to have hypolipidaemic properties.

The proprietary names listed in this monograph refer to preparations containing undefined or less readily defined heparinoids that are used in a range of conditions including musculoskeletal and joint disorders, haemorrhoids, lipid disorders, and thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fleboderma; Hemeran†; Hirudoid; ***Austral.:*** Hirudoid; Lasonil; ***Austria:*** Hemeran; Hirudoid; Lasonil; ***Belg.:*** Hemeran; Hirudoid; Lasonil; ***Braz.:*** Hirudoid; Topcoid; ***Chile:*** Hirudoid; ***Cz.:*** Heparoid; Hirudoid; ***Denm.:*** Hirudoid; ***Fin.:*** Hirudoid; ***Ger.:*** Etrat Sportsalbe MPS†; Hirudoid; Lasonil N†; Sanaven MPS; ***Gr.:*** Hemeran; Lasonil N; ***Hong Kong:*** Bruise Cream†; Hepacare; Hirudoid; ***Hung.:*** Hirudoid; ***India:*** Hirudoid; ***Indon.:*** Hirudoid; ***Ital.:*** Angioflux; Ateran†; Ateroid; Ateroxide; Condral; Erevan†; Glicamin†; Hirudoid; Lasonil†; Lasoven†; Matrix; ***Neth.:*** Hirudoid; Lasonil; ***Norw.:*** Hirudoid; ***NZ:*** Hirudoid; Lasonil; ***Philipp.:*** Hirudoid; ***Pol.:*** Hirudoid; ***Port.:*** Hemeran; Hirudoid; Lasonil; ***Rus.:*** Heparoid (Гепароид); ***Singapore:*** Hirudoid; ***Spain:*** Dinoven; Hirudoid; ***Swed.:*** Hirudoid; ***Switz.:*** Hemeran; Hirudoid; ***Thai.:*** Hirudoid; Varidoid; ***Turk.:*** Hirudoid; Lasonil; ***UK:*** Bruiseze; Hirudoid; Lasonil†; ***Venez.:*** Hirudoid.

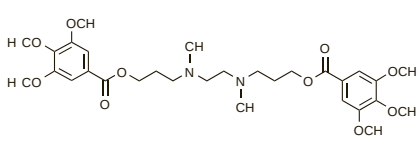
Multi-ingredient: ***Arg.:*** Mantus; ***Austral.:*** Movelat†; ***Austria:*** Lemuval; Mobilat; Mobilisin; Mobilisin plus; Moviflex; ***Belg.:*** Mobilat; Mobilisin; ***Braz.:*** Etrat†; Mobilat; Mobilisin Composto; ***Chile:*** Mobilat; Reparíven; ***Cz.:*** Ibu-Hepa; Ketazon Compositum†; Mobilat; ***Fin.:*** Mobilat; Moviflex†; ***Ger.:*** Dolo Mobilat†; Mobilat Aktiv; Mobilat†; Sanaven†; ***Gr.:*** Bayolin; ***Hong Kong:*** Mobilat†; Prelloran†; ***Hung.:*** Bayolin†; Mobilat N; Mobilisin†; ***Ital.:*** Flebs; Mobilat; Mobilisin; Momendol; Traumal†; ***Mex.:*** Mobilat; ***Neth.:*** Mobilat; ***NZ:*** Movelat†; ***Philipp.:*** Mobilat; ***Pol.:*** Helason; Ibalgin Sport; Lumbolin; Mobilat; ***Port.:*** Anacal; Mobilat; Mobilisin; Rimanal; ***Singapore:*** Mobilat†; ***Spain:*** Lasonil†; Movilat; Movilisin; ***Switz.:*** Dolo-Veniten†; Mobilat N; Mobilisin; Prelloran†; ***Thai.:*** Mobilat; Movelat†; ***UK:*** Anacal; Movelat; ***Venez.:*** Bargonil; Permucal.

Hexobendine *(BAN, USAN, rINN)*

Hexobendina; Hexobendinum.

Гексобендин

$C_{30}H_{44}N_2O_{10}$ = 592.7.
CAS — 54-03-5.
ATC — C01DX06.
ATC Vet — QC01DX06.



Hexobendine Hydrochloride *(BANM, rINNM)*

Hexobendine, Chlorhydrate d'; Hexobendini Hydrochloridum; Hidrocloruro de hexobendina; ST-7090. *NN*′-Ethylenebis(3-methylaminopropyl 3,4,5-trimethoxybenzoate) dihydrochloride.

Гексобендина Гидрохлорид

$C_{30}H_{44}N_2O_{10}$,2HCl = 665.6.
CAS — 50-62-4.
ATC — C01DX06.
ATC Vet — QC01DX06.

Profile

Hexobendine hydrochloride is a vasodilator that has been used in ischaemic heart disease. It is also included in multi-ingredient preparations used in cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ustimon.

Multi-ingredient: ***Austria:*** Instenon; ***Hong Kong:*** Instenon; ***Rus.:*** Instenon (Инстенон); ***Thai.:*** Instenon†.

Hirudin

Hirudina; Hirudine.

Profile

Hirudin is a 65-amino-acid protein that is a direct inhibitor of thrombin (see Lepirudin, p.1323). It has been extracted from leeches (p.1323) and this form is used in various topical preparations for peripheral vascular disorders. Recombinant hirudins, such as desirudin (p.1257) and lepirudin (p.1323) and analogues of hirudin, such as bivalirudin (p.1234), are used as anticoagulants.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Exhirud; ***Fr.:*** Hirucreme; ***Ger.:*** Exhirud†.

Multi-ingredient: ***Ger.:*** Haemo-Exhirud†; ***Ital.:*** Hirudex†.

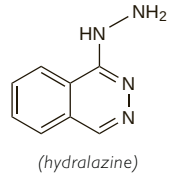
Hydralazine Hydrochloride

(BANM, rINNM)

Apressinum; Hidralazin-hidroklorid; Hidralazino hidrochloridas; Hidrocloruro de hidralazina; Hydralatsiinihydrokloridi; Hydralazin hydrochlorid; Hydralazin Hydrochloridum; Hydralazine, chlorhydrate d'; Hydralazinhydroklorid; Hydralazini hydrochloridum; Hydrallazine Hydrochloride; Idralazina. 1-Hydrazinophthalazine hydrochloride.

Гидралазина Гидрохлорид

$C_8H_8N_4$,HCl = 196.6.
CAS — 86-54-4 (hydralazine); 304-20-1 (hydralazine hydrochloride).
ATC — C02DB02.
ATC Vet — QC02DB02.



(hydralazine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Hydralazine Hydrochloride). A white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 3.5 to 4.2. Protect from light.
USP 31 (Hydralazine Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 500 of alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 3.5 to 4.2. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Discoloration of hydralazine injection was observed on several occasions after storage in a syringe for up to 12 hours.[1] Hydralazine reacts with metals and therefore the injection should be prepared using a nonmetallic filter and should be used as quickly as possible after being drawn through a needle into a syringe.

A study of the rate of degradation of hydralazine hydrochloride, 1 mg/mL in sweetened, aqueous oral liquids showed that glucose, fructose, lactose, and maltose reduced the stability of the drug.[2] In solutions containing mannitol or sorbitol, there was less than 10% degradation of hydralazine after 3 weeks. UK licensed product information states that contact with glucose causes hydralazine to be rapidly broken down and that hydralazine injection is therefore not compatible with glucose solutions.

1. Enderlin G. Discoloration of hydralazine injection. *Am J Hosp Pharm* 1984; **41:** 634.
2. Das Gupta V, *et al.* Stability of hydralazine hydrochloride in aqueous vehicles. *J Clin Hosp Pharm* 1986; **11:** 215–23.

Adverse Effects

Adverse effects are common with hydralazine, particularly tachycardia, palpitations, angina pectoris, severe headache, and gastrointestinal disturbances such as anorexia, nausea, vomiting, and diarrhoea. These adverse effects, and flushing, dizziness, and nasal congestion, which occur less often, may be seen at the start of treatment, especially if the dose is increased quickly. They generally subside with continued treatment. Other less common adverse effects include orthostatic hypoten-

sion, fluid retention with oedema and weight gain, conjunctivitis, lachrymation, tremor, and muscle cramps.

Hydralazine may deplete pyridoxine in the body, and can produce peripheral neuropathy with numbness and tingling of the extremities. Occasionally, hepatotoxicity, blood dyscrasias, haemolytic anaemia, difficulty in urinating, glomerulonephritis, constipation, paralytic ileus, depression, and anxiety occur.

Hypersensitivity reactions including fever, chills, pruritus, and rashes have been reported, and eosinophilia may occur.

Antinuclear antibodies may develop after prolonged use of large doses, and a condition resembling SLE may occur. The incidence is greater in slow acetylators, patients with renal impairment, women, and patients taking more than 100 mg of hydralazine daily. The symptoms usually disappear when the drug is withdrawn; some patients may require treatment with corticosteroids.

Acute overdosage may produce hypotension, tachycardia, myocardial ischaemia, arrhythmias, shock, and coma.

Carcinogenicity. Although earlier reports suggested that hydralazine might be carcinogenic, there was no evidence from a survey of 1978 patients with lung or colorectal cancer and 6807 controls that there was an increased risk of these neoplasms.[1]

1. Kaufman DW, *et al.* Hydralazine use in relation to cancers of the lung, colon, and rectum. *Eur J Clin Pharmacol* 1989; **36:** 259–64.

Effects on the blood. Three cases of thrombocytopenia were reported[1] in neonates whose mothers had been treated with hydralazine for some months before delivery. The thrombocytopenia and bleeding was transient with full recovery occurring within a few weeks. No adverse effects were noticed in the mothers.

1. Widerlöv E, *et al.* Hydralazine-induced neonatal thrombocytopenia. *N Engl J Med* 1980; **303:** 1235.

Effects on the cardiovascular system. Paradoxical severe hypertension developed after oral or intramuscular hydralazine on 3 occasions in a patient with renal artery stenosis.[1]

1. Webb DB, White JP. Hypertension after taking hydrallazine. *BMJ* 1980; **280:** 1582.

Effects on the kidneys. Rapidly progressive glomerulonephritis with focal and segmental lesions, usually accompanied by necrosis and crescent formation, has been reported in patients given hydralazine.[1-3] The condition is reported to be associated with the presence of antinuclear antibodies[3] and slow acetylator status,[2] factors associated with the development of hydralazine-induced lupus erythematosus.[4] However, renal involvement is much less common in drug-induced lupus,[4] and in a report of 15 such cases men and women and fast and slow acetylators were equally affected;[3] in addition the criteria for SLE were not usually fulfilled in these patients and it was suggested that the condition should be distinguished from lupus nephritis. Immediate withdrawal of hydralazine generally results in some improvement in renal function but complete recovery is uncommon; severe cases may require immunosuppressive therapy.[3]

1. Björck S, *et al.* Rapidly progressive glomerulonephritis after hydralazine. *Lancet* 1983; **ii:** 42.
2. Kincaid-Smith P, Whitworth JA. Hydralazine-associated glomerulonephritis. *Lancet* 1983; **ii:** 348.
3. Björck S, *et al.* Hydralazine-induced glomerulonephritis. *Lancet* 1985; **i:** 392.
4. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.

Effects on the skin. Pruritus and skin rashes have been reported with hydralazine use.

A 59-year-old woman who had been taking hydralazine 25 mg three times daily for 6 months developed symptoms of Sweet's syndrome (erythematous plaques and nodules and haemorrhagic blisters).[1] Symptoms began to subside on withdrawal of the drug but recurred on rechallenge. The condition resolved on discontinuation of hydralazine and treatment with prednisolone.

1. Gilmour E, *et al.* Drug-induced Sweet's syndrome (acute febrile neutrophilic dermatosis) associated with hydralazine. *Br J Dermatol* 1995; **133:** 490–1.

Lupus erythematosus. Lupus erythematosus is a well-documented adverse effect of hydralazine. Onset is typically delayed from 1 month to 5 years from the start of treatment, and the most common symptoms are arthralgia or arthritis, usually non-deforming, in up to 95% of patients, fever and myalgia in about 50%, and pleuropulmonary involvement, manifesting as pleurisy, pleural effusions, or pulmonary infiltrates in up to 30%.[1-3] Renal involvement is reported to be less common than in idiopathic SLE and there is some uncertainty as to whether the glomerulonephritis sometimes seen in patients receiving hydralazine should be considered lupus nephritis (see Effects on the Kidneys, above). Nonetheless, a 20% incidence of renal involvement has been reported.[1] Other complications and symptoms associated with lupus erythematosus in patients taking hydralazine include cutaneous vasculitis,[4-6] orogenital and cutaneous ulceration,[7] bilateral retinal vasculitis,[8] reactive hypoglycaemia (although the attribution is uncertain),[9] life-threatening cardiac tamponade,[10] and hoarseness and stridor secondary to vocal cord palsy, which progressed to respiratory arrest.[11] Skin rashes are reported to be less prominent than with the idiopathic form of the disease.[1] Fatalities have occurred,[12] but appear to be rare.

Estimates of the overall incidence of hydralazine-associated lupus erythematosus vary from about 1.2 to 5% or more.[13-16] The syndrome appears to occur only in patients who develop antinuclear antibodies while receiving hydralazine, but the incidence of positive antinuclear antibody tests is much higher than that of lupus, at up to 60%, so the presence of antinuclear antibodies alone is not diagnostic.[15] There is a strong relationship with drug dose,[14,16] acetylator status,[13,15,16] and patient gender,[16] the syndrome being more common in slow acetylators and women, and in patients receiving 100 mg daily or more.

Although it has been reported that hydralazine-associated lupus was more frequent in patients with the HLA-DR4 antigen[17] this was not confirmed by others[18] and subsequent work has suggested that the association is rather with the non-expressing or null forms of the adjacent complement C4 gene.[19] Hydralazine can inactivate complement C4 *in vitro*[20] and might exacerbate complement deficiency (which is known to be associated with idiopathic SLE) in patients with an already low level of C4 due to a null allele.[19]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.
2. Cohen MG, Prowse MV. Drug-induced rheumatic syndromes: diagnosis, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 199–218.
3. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; **12:** 283–90.
4. Bernstein RM, *et al.* Hydrallazine-induced cutaneous vasculitis. *BMJ* 1980; **280:** 156–7.
5. Peacock A, Weatherall D. Hydralazine-induced necrotising vasculitis. *BMJ* 1981; **282:** 1121–2.
6. Finlay AY, *et al.* Hydrallazine-induced necrotising vasculitis. *BMJ* 1981; **282:** 1703–4.
7. Neville E, *et al.* Orogenital ulcers, SLE and hydrallazine. *Postgrad Med J* 1981; **57:** 378–9.
8. Doherty M, *et al.* Hydralazine induced lupus syndrome with eye disease. *BMJ* 1985; **290:** 675.
9. Blackshear PJ, *et al.* Reactive hypoglycaemia and insulin autoantibodies in drug-induced lupus erythematosus. *Ann Intern Med* 1983; **99:** 182–4.
10. Anandadas JA, Simpson P. Cardiac tamponade, associated with hydralazine therapy, in a patient with rapid acetylator status. *Br J Clin Pract* 1986; **40:** 305–6.
11. Chong WK, *et al.* Acute laryngeal stridor with respiratory arrest in drug induced systemic lupus erythematosus. *BMJ* 1988; **297:** 660–1.
12. Sturman SG, *et al.* Fatal hydralazine-induced systemic lupus erythematosus. *Lancet* 1988; **ii:** 1304.
13. Bing RF, *et al.* Hydrallazine in hypertension: is there a safe dose? *BMJ* 1980; **281:** 353–4.
14. Freestone S, *et al.* Incidence of hydrallazine-associated autoimmune disease. *Br J Clin Pharmacol* 1982; **13:** 291P–292P.
15. Mansilla-Tinoco R, *et al.* Hydralazine, antinuclear antibodies, and the lupus syndrome. *BMJ* 1982; **284:** 936–9.
16. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. *BMJ* 1984; **289:** 410–12.
17. Batchelor JR, *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980; **i:** 1107–9.
18. Brand C, *et al.* Hydralazine-induced lupus: no association with HLA-DR4. *Lancet* 1984; **i:** 462.
19. Speirs C, *et al.* Complement system protein C4 and susceptibility to hydralazine-induced systemic lupus erythematosus. *Lancet* 1989; **i:** 922–4.
20. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; **ii:** 422–4.

Treatment of Adverse Effects

Withdrawal of hydralazine or dosage reduction reverses many of the adverse effects. Peripheral neuropathy has been reported to be alleviated by pyridoxine.

If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour of ingestion. Symptomatic and supportive treatment, including plasma expanders for shock and a beta blocker for tachycardia, should be given as necessary. Hypotension may respond to placing the patient in the supine position with the feet raised. If possible, pressor drugs should be avoided. If a pressor is necessary, one should be chosen that will not cause tachycardia or exacerbate arrhythmias; adrenaline should not be used.

Precautions

Hydralazine is contra-indicated in patients with severe tachycardia, dissecting aortic aneurysm, heart failure with high cardiac output, cor pulmonale, or myocardial insufficiency due to mechanical obstruction, for example aortic or mitral stenosis or constrictive pericarditis. Hydralazine is also contra-indicated in patients with idiopathic SLE and related disorders.

Hydralazine-induced vasodilatation produces myocardial stimulation. It should therefore be used with caution in patients with ischaemic heart disease since it can increase angina and it should not be given after myocardial infarction until the patient's condition has stabilised. Patients with suspected or confirmed ischaemic heart disease should be given hydralazine under cover of a beta blocker, which should be started a few days before hydralazine, in order to prevent myocardial stimulation. If given to patients with heart failure they should be monitored for orthostatic hypotension and tachycardia during the initial stages of therapy, preferably in hospital. If treatment with hydralazine is to be stopped in patients with heart failure it should generally be withdrawn gradually. Hydralazine should be used with caution in patients with cerebrovascular disorders.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment. Complete blood counts and antinuclear antibody determinations should be carried out about every 6 months during long-term therapy. Urine analysis (for microhaematuria and proteinuria) is also recommended.

Hydralazine is teratogenic in some species of *animals* and should therefore be avoided during the first two trimesters of pregnancy.

Patients may experience impaired reactions, especially at the start of therapy, and should not drive or operate machinery if affected.

Breast feeding. Hydralazine is distributed into breast milk in small amounts (see Pregnancy, below) but no adverse effects have been seen in infants and the American Academy of Pediatrics therefore considers[1] hydralazine to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. Hydralazine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Hydralazine should be avoided during the first two trimesters of pregnancy.

Hydralazine concentrations were found to be similar in maternal and umbilical-cord blood in a study of 6 women being treated with hydralazine for pronounced hypertension during pregnancy.[1] Hydralazine was determined in the breast milk of 1 mother, but amounts detected were unlikely to produce clinically relevant concentrations in the infant.

For a report of thrombocytopenia occurring in neonates following maternal treatment with hydralazine during pregnancy, see Effects on the Blood under Adverse Effects, above.

1. Liedholm H, *et al.* Transplacental passage and breast milk concentrations of hydralazine. *Eur J Clin Pharmacol* 1982; **21:** 417–19.

Interactions

The hypotensive effect of hydralazine may be enhanced by other drugs with a hypotensive action. Severe hypotension may occur if hydralazine and diazoxide are given together. However, some interactions with antihypertensives may be beneficial: thiazide diuretics also counteract the fluid retention caused by hydralazine, and beta blockers diminish the cardiac-accelerating effects.

Indometacin. A study[1] in 9 healthy subjects found that indometacin 100 mg daily did not lessen the hypotensive effect of hydralazine. However, another study[2] showed that indometacin 200 mg daily, while having no effect on heart rate, renal or limb blood flow, or plasma-catecholamine concentration, did reduce the hypotensive effect of hydralazine.

1. Jackson SHD, Pickles H. Indomethacin does not attenuate the effects of hydralazine in normal subjects. *Eur J Clin Pharmacol* 1983; **25:** 303–5.
2. Cinquegrani MP, Liang C. Indomethacin attenuates the hypotensive action of hydralazine. *Clin Pharmacol Ther* 1986; **39:** 564–70.

Pharmacokinetics

Hydralazine given orally is rapidly absorbed from the gastrointestinal tract but undergoes considerable first-pass metabolism by acetylation in the gastrointestinal mucosa and liver. The rate of metabolism is genetically determined and depends upon the acetylator status of the individual. The bioavailability of hydralazine has

been reported to be about 35% in slow acetylators and less in fast acetylators; thus plasma concentrations after a given dose are higher in slow acetylators.

Peak plasma concentrations have been reported to occur after about one hour. Hydralazine is chiefly present in plasma as a hydrazone conjugate with pyruvic acid. Plasma protein binding is about 90%. The drug is widely distributed, notably into arterial walls.

Systemic metabolism in the liver is by hydroxylation of the ring system and conjugation with glucuronic acid; most sources suggest that *N*-acetylation is not of major importance in systemic clearance and that therefore acetylator status does not affect elimination. Hydralazine is excreted mainly in urine as metabolites.

The apparent average half-life for hydralazine has been reported to vary from about 45 minutes to about 8 hours, with a number of sources giving the average as about 2 to 4 hours. Some of the variation may be due to problems with the analytical procedures—see below. The half-life is prolonged in renal impairment and may be up to 16 hours in patients with a creatinine clearance of less than 20 mL/minute.

Hydralazine crosses the placenta and is distributed into breast milk.

◊ Attempts to describe the pharmacokinetics of hydralazine have been complicated by the instability of the drug itself in plasma and in alkaline solutions, and the instability of its circulating metabolites during analysis. This has meant that many techniques for the measurement of hydralazine have proved non-selective and yield overestimates of unchanged drug.[1] Studies using less selective methods have yielded an apparent bioavailability for oral hydralazine of 38 to 69% in slow acetylators and 22 to 32% in fast acetylators; in contrast, more selective assays have yielded values of 31 to 35% and 10 to 16% for slow and rapid acetylators respectively. Similarly, hydralazine plasma clearance is lower and the half-life longer when based upon the results of non-selective assay procedures; mean elimination half-life has ranged from 2.2 to 3.6 hours based upon these methods compared with 0.67 to 0.96 hours using a more selective assay. Improved pharmacokinetic data has indicated that while the first-pass effect is dependent upon acetylator phenotype, systemic clearance is only minimally dependent upon acetylation. The formation of the pyruvic acid hydrazone, which is without significant vasodilator activity, contributes to extrahepatic phenotype-independent clearance.

Although some workers have correlated the hypotensive effect of hydralazine with concentrations,[2] others have been unable to do so.[3] Moreover, the duration of hypotensive effect has been shown to exceed considerably that predicted from the rate of elimination.[4,5] Possible explanations are the accumulation of hydralazine at its sites of action in the arterial walls[6] or the existence of active metabolites.[7-9]

Concurrent intake of food has been found to enhance considerably the bioavailability of hydralazine[10] but food-related reductions in plasma-hydralazine concentrations with reduced vasodilator effect have also been reported.[11] The discrepancy was thought to be due to the greater specificity of the assay used in the latter study and to differences in the timing of food and hydralazine administration in the two studies.[12,13]

1. Ludden TM, *et al.* Clinical pharmacokinetics of hydralazine. *Clin Pharmacokinet* 1982; **7:** 185–205.
2. Zacest R, Koch-Weser J. Relation of hydralazine plasma concentration to dosage and hypotensive action. *Clin Pharmacol Ther* 1972; **13:** 420–5.
3. Talseth T, *et al.* Hydralazine slow-release: observations on serum profile and clinical efficacy in man. *Curr Ther Res* 1977; **21:** 157–68.
4. O'Malley K, *et al.* Duration of hydralazine action in hypertension. *Clin Pharmacol Ther* 1975; **18:** 581–6.
5. Shepherd AMM, *et al.* Hydralazine kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1980; **28:** 804–11.
6. Moore-Jones D, Perry HM. Radioautographic localization of hydralazine-1-C in arterial walls. *Proc Soc Exp Biol Med* 1966; **122:** 576–9.
7. Barron K, *et al.* Comparative evaluation of the in vitro effects of hydralazine and hydralazine acetonide on arterial smooth muscle. *Br J Pharmacol* 1977; **61:** 345–9.
8. Haegele KD, *et al.* Identification of hydrallazine and hydrallazine hydrazone metabolites in human body fluids and quantitative in vitro comparisons of their smooth muscle relaxant activity. *Br J Clin Pharmacol* 1978; **5:** 489–94.
9. Reece PA, *et al.* Interference in assays for hydralazine in humans by a major plasma metabolite, hydralazine pyruvic acid hydrazone. *J Pharm Sci* 1978; **67:** 1150–3.
10. Melander A, *et al.* Enhancement of hydralazine bioavailability by food. *Clin Pharmacol Ther* 1977; **22:** 104–7.
11. Shepherd AMM, *et al.* Effect of food on blood hydralazine levels and response in hypertension. *Clin Pharmacol Ther* 1984; **36:** 14–18.
12. Melander A, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; **38:** 475.
13. Shepherd AMM, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; **38:** 475–6.

Uses and Administration

Hydralazine is a direct-acting vasodilator that acts mainly on the arterioles. It reduces blood pressure and peripheral resistance but produces fluid retention. Tachycardia and an increase in cardiac output occur mainly as a reflex response to the reduction in peripheral resistance. Hydralazine tends to improve renal and cerebral blood flow and its effect on diastolic pressure is more marked than on systolic pressure.

Hydralazine hydrochloride is given orally for the treatment of hypertension (p.1171), usually with a beta blocker and a thiazide diuretic. In addition to an additive antihypertensive effect, this combination reduces the reflex tachycardia and fluid retention caused by hydralazine. Hydralazine may be given intravenously in hypertensive crises. It is also used with isosorbide dinitrate in the management of heart failure (but see Precautions, above). For further discussion of this use of hydralazine, see below.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment.

In **hypertension**, the usual initial oral dose of hydralazine hydrochloride is 40 to 50 mg daily in divided doses, increased according to response. In the UK it is recommended that the dose should not be increased above 100 mg daily without checking acetylator status, although the recommended maximum dose for hypertension is 200 mg daily; doses above 100 mg daily are associated with an increased incidence of lupus erythematosus, particularly in women and in slow acetylators.

In hypertensive crises, hydralazine hydrochloride is given in doses of 5 to 10 mg by slow intravenous injection, repeated if necessary after 20 to 30 minutes. Alternatively, it may be given by continuous intravenous infusion in an initial dose of 200 to 300 micrograms/minute; the usual maintenance dose range is 50 to 150 micrograms/minute. Hydralazine hydrochloride has also been given by intramuscular injection.

For **heart failure** in self-identified black patients, hydralazine may be given as an oral combination preparation with isosorbide dinitrate; the dose is 37.5 mg of hydralazine with 20 mg of isosorbide dinitrate three times daily, and may be doubled if necessary.

Heart failure. Hydralazine with isosorbide dinitrate may have a role in the management of patients with heart failure (p.1165) who remain symptomatic despite standard therapy or in whom standard therapy is contra-indicated or not tolerated. Although a meta-analysis of a number of studies[1] of vasodilator therapy for heart failure failed to show a benefit in terms of improved functional status or reduced mortality in patients given hydralazine alone, there is evidence from the Veterans Administration Cooperative Study[2] of reduced mortality from the use of hydralazine with nitrates. This has been confirmed in a second study (V-HeFTII),[3] although hydralazine with isosorbide dinitrate was less effective than enalapril. Subgroup analysis suggested that the effect might be greater in black patients, and a later study[4] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality.

Hydralazine has also been tried in children with heart failure,[5,6] but experience is limited.

1. Mulrow CD, *et al.* Relative efficacy of vasodilator therapy in chronic congestive heart failure: implications of randomized trials. *JAMA* 1988; **259:** 3422–6.
2. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration cooperative study. *N Engl J Med* 1986; **314:** 1547–52.
3. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325:** 303–10.
4. Taylor AL, *et al.* Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049–57. Correction. *ibid.* 2005; **352:** 1276.
5. Artman M, *et al.* Hemodynamic effects of hydralazine in infants with idiopathic dilated cardiomyopathy and congestive heart failure. *Am Heart J* 1987; **113:** 144–50.
6. Rao PS, Andaya WG. Chronic afterload reduction in infants and children with primary myocardial disease. *J Pediatr* 1986; **108:** 530–4.

Preparations

BP 2008: Hydralazine Injection; Hydralazine Tablets;
USP 31: Hydralazine Hydrochloride Injection; Hydralazine Hydrochloride Oral Solution; Hydralazine Hydrochloride Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Hidral; Hydrapres; ***Austral.:*** Alphapress; Apresoline; ***Braz.:*** Apresolina; Nepresol; ***Canad.:*** Apresoline; Novo-Hylazin; Nu-Hydral; ***Hong Kong:*** Apresoline†; ***Irl.:*** Apresoline; ***Mex.:*** Apresolina; Bionobal; ***Norw.:*** Apresolin; ***NZ:*** Apresoline; ***Philipp.:*** Apresoline; ***S.Afr.:*** Apresoline; Hyperphen; ***Spain:*** Hydrapres; ***Swed.:*** Apresolin; ***Thai.:*** Apresoline; Cesoline; ***UK:*** Apresoline; ***USA:*** Apresoline; ***Venez.:*** Apresolina†.

Multi-ingredient: ***Austria:*** Polinorm; Trepress; Triloc; ***Ger.:*** Docidrazin†; Impresso†; Pertenso N; Treloc; Trepress; TRI-Normin; ***India:*** Corbetazine; ***Indon.:*** Ser-Ap-Es; ***Spain:*** Betadipresan Diu†; Betadipresan†; Neatenol Diuvas; Tensiocomplet; ***Thai.:*** Hydrares; Hypery†; Mano-Ap-Es; Reser; Ser-Ap-Es; ***USA:*** Apresazide†; BiDil; Hydra-zide; Hydrap-ES†; Marpres; Ser-Ap-Es†; Tri-Hydroserpine†.

Hydrochlorothiazide *(BAN, rINN)* ⊗

Hidroclorotiazidas; Hidroclorotiazida; Hidroklorotiazid; Hydrochlorothiazid; Hydrochlorothiazidum; Hydrochlorotiazyd; Hydrokloorittiatsidi; Hydroklortiazid. 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

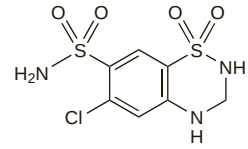
Гидрохлоротиазид

$C_7H_8ClN_3O_4S_2$ = 297.7.

CAS — 58-93-5.

ATC — C03AA03.

ATC Vet — QC03AA03.



NOTE. Compounded preparations of hydrochlorothiazide may be represented by the following names:

- Co-amilozide (*BAN*)—hydrochlorothiazide 10 parts and amiloride hydrochloride 1 part (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide
- Co-triamterzide (*BAN*)—triamterene 2 parts and hydrochlorothiazide 1 part (w/w)
- Co-triamterzide (*PEN*)—triamterene and hydrochlorothiazide
- Co-zidocapt (*BAN*)—hydrochlorothiazide 1 part and captopril 2 parts (w/w).

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

Ph. Eur. 6.2 (Hydrochlorothiazide). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Hydrochlorothiazide). A white or practically white, practically odourless crystalline powder. Slightly soluble in water; insoluble in chloroform, in ether, and in dilute mineral acids; freely soluble in dimethylformamide, in *n*-butylamine, and in sodium hydroxide solution; sparingly soluble in methyl alcohol.

Adverse Effects

Hydrochlorothiazide and other thiazide diuretics may cause a number of metabolic disturbances especially at high doses. They may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. They may cause hyperuricaemia and precipitate attacks of gout in some patients. Thiazide diuretics may be associated with electrolyte imbalances including hypochloraemic alkalosis, hyponatraemia, and hypokalaemia. Hypokalaemia intensifies the effect of digitalis on cardiac muscle and treatment with digitalis or its glycosides may have to be temporarily suspended. Patients with cirrhosis of the liver are particularly at risk from hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses in conjunction with restricted salt in the diet. The urinary excretion of calcium is reduced. Hypomagnesaemia has also occurred. Adverse changes in plasma lipids have also been noted but their clinical significance is unclear.

Signs of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain and cramps, seizures, oliguria, hypotension, and gastrointestinal disturbances.