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.

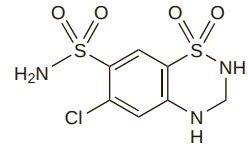
Гидрохлоротиазид

$C_7H_8ClN_3O_4S_2$ = 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.

Other adverse effects include anorexia, gastric irritation, nausea, vomiting, constipation, diarrhoea, sialadenitis, headache, dizziness, photosensitivity reactions, orthostatic hypotension, paraesthesia, impotence, and yellow vision. Hypersensitivity reactions include skin rashes, fever, pulmonary oedema, pneumonitis, anaphylaxis, and toxic epidermal necrolysis. Cholestatic jaundice, pancreatitis, and blood dyscrasias including thrombocytopenia and, more rarely, granulocytopenia, leucopenia, and aplastic and haemolytic anaemia have been reported.

Intestinal ulceration has occurred after the use of tablets containing thiazides with an enteric-coated core of potassium chloride (see also under Potassium, p.1684).

Carcinogenicity. Several studies have suggested that long-term diuretic therapy may be associated with the development of cancer. A meta-analysis[1] of 9 case control studies and 3 cohort studies found an increased risk of renal cell carcinoma in patients receiving diuretics, and a further retrospective study[2] found that the risk of colon cancer was also increased. While the risk is probably not significant in most patients, it was suggested[1,2] that it should be taken into consideration when choosing long-term therapy for younger patients.

1. Grossman E, *et al.* Does diuretic therapy increase the risk of renal cell carcinoma? *Am J Cardiol* 1999; **83:** 1090–3.
2. Tenenbaum A, *et al.* Is diuretic therapy associated with an increased risk of colon cancer? *Am J Med* 2001; **110:** 143–5.

Effects on the blood. There have been case reports of intravascular immune haemolysis in patients taking hydrochlorothiazide and methyldopa.[1-3] In each of these 3 cases the hydrochlorothiazide was identified as the probable cause of haemolysis on serological data, although methyldopa could have been a contributory factor. One of these patients died[3] during the haemolytic episode although post-mortem examination failed to reveal a cause of death.

1. Vila JM, *et al.* Thiazide-induced immune hemolytic anemia. *JAMA* 1976; **236:** 1723–4.
2. Garratty G, *et al.* Acute immune intravascular hemolysis due to hydrochlorothiazide. *Am J Clin Pathol* 1981; **76:** 73–8.
3. Beck ML, *et al.* Fatal intravascular immune hemolysis induced by hydrochlorothiazide. *Am J Clin Pathol* 1984; **81:** 791–4.

Effects on electrolyte balance. ***MAGNESIUM AND POTASSIUM.*** The clinical consequences of diuretic-induced hypokalaemia have been controversial.[1-3] Of major concern has been the possibility that diuretic-induced hypokalaemia could predispose to cardiac arrhythmias and sudden cardiac death in some patients, and it has been suggested that this could explain the lower than expected reduction in deaths due to ischaemic heart disease found in some hypertension trials. Indeed, some case-control studies[4,5] have suggested an association between an increased risk of sudden cardiac death and the use of thiazides or other non-potassium-sparing diuretics; the addition of a potassium supplement had little effect on this risk, whereas addition of a potassium-sparing diuretic to the thiazide lowered the risk.[4] However, no reduction in cardiac arrhythmias after the correction of hypokalaemia has been seen[6] nor any evidence of increased arrhythmias associated with diuretic-induced hypokalaemia.[7] Several reviews[8,9] have argued that there is no proof of a causal relationship between hypokalaemia and serious dysrhythmias and this was endorsed by a randomised study.[10]

It is generally agreed that routine potassium supplementation in patients taking diuretics is unnecessary; however, supplementation will be required if the serum-potassium concentration falls below 3.0 mmol/litre. Potassium replacement or conservation is also likely to be necessary in patients at risk from the cardiac effects of hypokalaemia[11] such as those with severe heart disease, those taking digitalis preparations or high doses of diuretics, and in patients with severe liver disease.

The amount of potassium in fixed combination diuretic and potassium preparations has long been considered insufficient to correct hypokalaemia and the effectiveness of oral potassium supplements in increasing body stores of potassium has been questioned.[12-14] Hypokalaemia may be overcome by adding a potassium-sparing diuretic such as amiloride or triamterene[15] to the regimen, but there is a danger of hyperkalaemia if they are used indiscriminately. The *routine* use of fixed-dose combination preparations of a thiazide or loop diuretic with a potassium-sparing diuretic is considered unnecessary.[16] Potassium-sparing diuretics will not correct the potassium deficit unrelated to diuretic therapy in patients with severe heart failure.[17] When thiazides are given with drugs that may induce hyperkalaemia, such as beta blockers, ACE inhibitors, or angiotensin II receptor antagonists, the diuretic-induced hypokalaemia may be ameliorated, but not necessarily corrected completely. Hypokalaemia has been reported[18-20] in patients taking fixed-dose combinations of thiazides and beta blockers.

Potassium supplementation alone may not be sufficient to correct hypokalaemia in patients who are also deficient in magnesium,[21] although it is unlikely to be of clinical significance.[22]

Magnesium depletion has also been implicated as a risk factor for arrhythmias.[9,23]

1. Materson BJ. Diuretic-associated hypokalemia. *Arch Intern Med* 1985; **145:** 1966–7.
2. Kaplan NM, *et al.* Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 1985; **312:** 746–9.
3. Kassirer JP, Harrington JT. Fending off the potassium pushers. *N Engl J Med* 1985; **312:** 785–7.
4. Siscovick DS, *et al.* Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994; **330:** 1852–7.
5. Hoes AW, *et al.* Diuretics, β-blockers, and the risk for sudden cardiac death in hypertensive patients. *Ann Intern Med* 1995; **123:** 481–7.
6. Papademetriou V, *et al.* Diuretic-induced hypokalemia in uncomplicated systemic hypertension: effect of plasma potassium correction on cardiac arrhythmias. *Am J Cardiol* 1983; **52:** 1017–22.
7. Papademetriou V, *et al.* Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. *Arch Intern Med* 1988; **148:** 1272–6.
8. Harrington JT, *et al.* Our national obsession with potassium. *Am J Med* 1982; **73:** 155–9.
9. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; **149**: 2640–8.
10. Siegel D, *et al.* Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 1992; **267:** 1083–9.
11. Anonymous. Potassium-sparing diuretics—when are they really needed? *Drug Ther Bull* 1985; **23:** 17–20.
12. Jackson PR, *et al.* Relative potency of spironolactone, triamterene and potassium chloride in thiazide-induced hypokalaemia. *Br J Clin Pharmacol* 1982; **14:** 257–63.
13. Shenfield GM. Fixed combination drug therapy. *Drugs* 1982; **23:** 462–80.
14. Papademetriou V, *et al.* Effectiveness of potassium chloride or triamterene in thiazide hypokalemia. *Arch Intern Med* 1985; **145:** 1986–90.
15. Kohvakka A. Maintenance of potassium balance during long-term diuretic therapy in chronic heart failure patients with thiazide-induced hypokalemia: comparison of potassium supplementation with potassium chloride and potassium-sparing agents, amiloride and triamterene. *Int J Clin Pharmacol Ther Toxicol* 1988; **26:** 273–7.
16. Anonymous. Routine use of potassium-sparing diuretics. *Drug Ther Bull* 1991; **29:** 85–7.
17. Davidson C, *et al.* The effects of potassium supplements, spironolactone or amiloride on the potassium status of patients with heart failure. *Postgrad Med J* 1978; **54:** 405–9.
18. Skehan JD, *et al.* Hypokalaemia induced by a combination of a beta-blocker and a thiazide. *BMJ* 1982; **284:** 83.
19. Odugbesan O, *et al.* Hazards of combined beta-blocker/diuretic tablets. *Lancet* 1985; **i:** 1221–2.
20. Jacobs L. Hypokalaemia with beta-blocker/thiazide combinations. *J R Coll Gen Pract* 1986; **36:** 39.
21. Dyckner T. Relation of cardiovascular disease to potassium and magnesium deficiencies. *Am J Cardiol* 1990; **65:** 44–6.
22. Papademetriou V. Magnesium depletion and thiazide hypokalemia. *Arch Intern Med* 1986; **146:** 1026.
23. Ryan MP. Diuretics and potassium/magnesium depletion: directions for treatment. *Am J Med* 1987; **82** (suppl 3A): 38–47.

SODIUM. Diuretics are a common cause of hyponatraemia.[1-5] Dilutional hyponatraemia may occur in patients with heart failure, but hyponatraemia may also result from sodium depletion[1] or inappropriate antidiuretic hormone secretion.[6] Other suggested mechanisms include decreased renal clearance of free water, hypomagnesaemia, and intracellular potassium depletion.[3,7] There have been a number of reports suggesting that hyponatraemia may be a particular problem with combinations of hydrochlorothiazide and potassium-sparing diuretics,[8-10] especially in elderly patients. The effect may be exacerbated by the relatively high doses of thiazide present in some fixed-dose preparations.[11] The symptoms of hyponatraemia may be non-specific and include nausea, lethargy, weakness, mental confusion, and anorexia,[1,2] but it may be an important cause of morbidity.[2,7] Severe sequelae of hyponatraemia include tonic-clonic seizures[12] and clinical features resembling subarachnoid haemorrhage.[13,14] Some patients, especially the elderly, may be particularly susceptible to the hyponatraemic effects of thiazides, possibly as a result of inappropriate secretion of antidiuretic hormone.[6] Plasma electrolyte concentrations should be monitored in patients taking long-term diuretic therapy.[3,12] Measurement of serum-sodium concentration and body-weight after a single dose of thiazide could be useful in identifying patients at increased risk of developing hyponatraemia.[7]

1. Roberts CJC, *et al.* Hyponatraemia: adverse effect of diuretic treatment. *BMJ* 1977; **1:** 210.
2. Kennedy PGE, *et al.* Severe hyponatraemia in hospital inpatients. *BMJ* 1978; **2:** 1251–3.
3. Walters EG, *et al.* Hyponatraemia associated with diuretics. *Br J Clin Pract* 1987; **41:** 841–4.
4. Spital A. Diuretic-induced hyponatremia. *Am J Nephrol* 1999; **19:** 447–52.
5. Mann SJ. The silent epidemic of thiazide-induced hyponatremia. *J Clin Hypertens (Greenwich)* 2008; **10:** 477–84.
6. Sonnenblick M, *et al.* Thiazide-induced hyponatremia and vasopressin release. *Ann Intern Med* 1989; **110:** 751.
7. Friedman E, *et al.* Thiazide-induced hyponatremia: reproducibility by single dose rechallenge and an analysis of pathogenesis. *Ann Intern Med* 1989; **110:** 24–30.
8. Strykers PH, *et al.* Hyponatremia induced by a combination of amiloride and hydrochlorothiazide. *JAMA* 1984; **252:** 389.
9. Roberts CJC, *et al.* Hyponatraemia induced by a combination of hydrochlorothiazide and triamterene. *BMJ* 1984; **288:** 1962.
10. Millson D, *et al.* Hyponatraemia and Moduretic (amiloride plus hydrochlorothiazide). *BMJ* 1984; **289:** 1308–9.
11. Bayer AJ, *et al.* Plasma electrolytes in elderly patients taking fixed combination diuretics. *Postgrad Med J* 1986; **62:** 159–62.
12. Johnston C, *et al.* Hyponatraemia and Moduretic-grand mal seizures: a review. *J R Soc Med* 1989; **82:** 479–83.
13. Benfield GFA, *et al.* Dilutional hyponatraemia masquerading as subarachnoid haemorrhage in patient on hydrochlorothiazide/amiloride/timolol combined drug. *Lancet* 1986; **ii:** 341.
14. Bain PG, *et al.* Thiazide-induced dilutional hyponatraemia masquerading as subarachnoid haemorrhage. *Lancet* 1986; **ii:** 634.

Effects on the gallbladder. There is an increased risk of cholecystitis in patients taking thiazides, with some indication that risk increases with the duration of use;[1,2] some workers concluded that this increased risk was confined to patients with pre-existing gallstones.[2] In a study in 10 healthy subjects,[3] hydrochlorothiazide was found to induce modest changes in biliary lipid concentrations although it was not associated with supersaturation of the bile. These changes could not wholly explain any increase in gallbladder disease in patients taking thiazides. However, evidence is conflicting; other studies[4,5] have found no association between thiazides and cholecystitis, except possibly in women who are not overweight.[5]

1. Rosenberg L, *et al.* Thiazides and acute cholecystitis. *N Engl J Med* 1980; **303:** 546–8.
2. van der Linden W, *et al.* Acute cholecystitis and thiazides. *BMJ* 1984; **289:** 654–5.
3. Angelin B. Effect of thiazide treatment on biliary lipid composition in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 95–6.
4. Porter JB, *et al.* Acute cholecystitis and thiazides. *N Engl J Med* 1981; **304:** 954–5.
5. Kakar F, *et al.* Thiazide use and the risk of cholecystectomy in women. *Am J Epidemiol* 1986; **124:** 428–33.

Effects on glucose metabolism. The adverse effects of thiazides on glucose metabolism, such as insulin resistance, impaired glucose tolerance, precipitation of overt diabetes, and worsening of diabetic control, are well established but appear to be dose-related and may not be significant at lower doses (for example, hydrochlorothiazide 6.25 or 12.5 mg).[1] A study[2] in 16 non-diabetic hypertensive patients found that bendroflumethiazide, in a dose of 1.25 mg daily, had no effect on insulin sensitivity whereas a daily dose of 5 mg produced hepatic insulin resistance. Similarly, the high doses, for example bendroflumethiazide 5 mg twice daily, used in the Medical Research Council Study on Mild to Moderate Hypertension[3] resulted in an incidence of glucose intolerance that led to withdrawal from the study of 9.38 per 1000 patient-years in men and 6.01 per 1000 patient-years in women compared with 2.51 and 0.82 per 1000 patient-years respectively in patients taking placebo. A later prospective study[4] in non-diabetic hypertensive patients found that those taking thiazides [doses not specified] were at no greater risk for developing diabetes than those not receiving antihypertensive therapy. However, a prospective cohort study[5] in men aged between 50 and 60 found that those taking antihypertensive treatment (mainly thiazides, beta blockers, or both) showed an increase in blood-glucose concentrations which was an independent risk factor for myocardial infarction, even when baseline insulin resistance was accounted for. Another prospective study[6] of 3 cohorts of men or women also found that use of thiazides was independently associated with a higher risk of diabetes.

It has been suggested[7] that the effect of thiazides on glucose metabolism is related to their effect on potassium and that control of hypokalaemia may prevent the development of diabetes, but this remains to be confirmed.

1. Neutel JM. Metabolic manifestations of low-dose diuretics. *Am J Med* 1996; **101** (suppl 3A): 71S–82S.
2. Harper R, *et al.* Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension. *BMJ* 1994; **309:** 226–30.
3. Greenburg G. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; **ii:** 539–43.
4. Gress TW, *et al.* Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 905–12.
5. Dunder K, *et al.* Increase in blood glucose concentration during antihypertensive treatment as a predictor of myocardial infarction: population based cohort study. *BMJ* 2003; **326:** 681–4.
6. Taylor EN, *et al.* Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; **29:** 1065–70.
7. Zillich AJ, *et al.* Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006; **48:** 219–24.

Effects on the kidneys. Thiazides can produce acute renal failure either from over-enthusiastic use producing sodium depletion and hypovolaemia or, occasionally, as a result of a hypersensitivity reaction.[1] Acute interstitial nephritis has been reported.[2,3] They can occasionally cause the formation of non-opaque urate calculi.[4]

1. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: I. *BMJ* 1977; **2:** 242–4.
2. Linton AL, *et al.* Acute interstitial nephritis due to drugs: review of the literature with a report of nine cases. *Ann Intern Med* 1980; **93:** 735–41.
3. Anonymous. Case records of the Massachusetts General Hospital: case 42-1983. *N Engl J Med* 1983; **309:** 970–8.
4. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: II. *BMJ* 1977; **2:** 375–7.

Effects on lipid metabolism. Thiazides have been reported to adversely affect the plasma-lipid profile in the short term by increasing concentrations of low-density and very-low-density lipoprotein cholesterol, as well as of triglycerides, but not of high-density lipoprotein cholesterol.[1] These effects are probably dose-related[2] and it has been argued that changes in plasma lipids

are likely to be slight at the relatively low doses now used in hypertension. There is some evidence to suggest that these lipid changes may not persist long-term.[3] In the Treatment of Mild Hypertension Study (TOMHS),[4] plasma total cholesterol concentrations were increased after 12 months in patients receiving chlortalidone but this effect was no longer present after 24 months. Although there has been concern that any hyperlipidaemic effect might offset the benefits of treating hypertension in patients at risk of ischaemic heart disease, studies such as ALLHAT[5] have shown that thiazide-like diuretics (in this case chlortalidone) are as effective as other antihypertensives in reducing the incidence of cardiovascular events in patients with hypertension and at least one other risk factor for ischaemic heart disease.

1. Ames R. Effects of diuretic drugs on the lipid profile. *Drugs* 1988; **36** (suppl 2): 33–40.
2. Carlsen JE, *et al.* Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990; **300:** 975–8.
3. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; **149:** 2640–8.
4. Grimm RH, *et al.* Long-term effects on plasma lipids of diet and drugs to treat hypertension. *JAMA* 1996; **275:** 1549–56.
5. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.* 2003; **289:** 178.

Effects on the nervous system. A 40-year old woman appeared sleepy and confused 1 week after starting hydrochlorothiazide.[1] Although her plasma-potassium concentrations had fallen they were still in the normal range, and it was concluded that her symptoms were due to an adverse reaction to the drug itself.

1. Daugherty KK, Subramanian J. Cognitive and neurologic impairment with hydrochlorothiazide. *Am J Health-Syst Pharm* 2005; **62:** 2630–3.

Effects on respiratory function. Acute interstitial pneumonitis and acute pulmonary oedema are rare but potentially dangerous complications of thiazides and may be due to a hypersensitivity reaction. Several cases have been reported,[1-7] frequently after a single dose of hydrochlorothiazide or chlorothiazide. The presenting symptoms could be mistakenly attributed to myocardial infarction.

1. Steinberg AD. Pulmonary edema following ingestion of hydrochlorothiazide. *JAMA* 1968; **204:** 167–9.
2. Beaudry C, Laplante L. Severe allergic pneumonitis from hydrochlorothiazide. *Ann Intern Med* 1973; **78:** 251–3.
3. Parfrey NA, Herlong HF. Pulmonary oedema after hydrochlorothiazide. *BMJ* 1984; **288:** 1880.
4. Watrigant Y, *et al.* Pneumopathie à l'hydrochlorothiazide d'évolution subaiguë: etude cytologique du lavage broncho-alvéolaire. *Rev Mal Respir* 1986; **4:** 227–9.
5. Klein MD. Noncardiogenic pulmonary edema following hydrochlorothiazide ingestion. *Ann Emerg Med* 1987; **16:** 901–3.
6. Bowden FJ. Non-cardiogenic pulmonary oedema after ingestion of chlorothiazide. *BMJ* 1989; **298:** 605.
7. Bernal C, Patarca R. Hydrochlorothiazide-induced pulmonary edema and associated immunologic changes. *Ann Pharmacother* 1999; **33:** 172–4.

Effects on sexual function. Adverse effects on sexual function have been reported in hypertensive patients given thiazides and other antihypertensives but it is not clear how much this is due to the underlying disease and how much is due to the drugs. In the Treatment of Mild Hypertension Study (TOMHS),[1] a double-blind randomised controlled trial that allocated patients to treatment with one of five groups of antihypertensives, the incidence of erectile dysfunction in men was relatively low but was highest in the diuretic group (chlortalidone treatment). The incidence was significantly higher in chlortalidone recipients than in placebo recipients at 24 months (17.1 and 8.1% respectively), but the difference was no longer significant at 48 months (18.3 and 16.7% respectively).

1. Grimm RH, *et al.* Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: Treatment of Mild Hypertension Study (TOMHS). *Hypertension* 1997; **29:** 8–14.

Effects on the skin. Rashes and skin reactions have been reported in patients taking thiazides. *Photosensitivity* reactions are among the most frequently reported skin reactions. In Australia[1] co-amilozide was the preparation most commonly implicated in photosensitivity reactions in reports to the Australian Drug Reactions Advisory Committee, although this may reflect the high usage of this preparation. The most likely mechanism is thought to be phototoxicity[1,2] involving mainly UVA radiation although UVB may be involved in some cases.[2] Chronic photosensitivity does not usually occur after stopping the drug[2] although photosensitivity may persist for longer in some patients than in others.[2,3] Eruptions resembling *lichen planus*[4] and *subacute cutaneous lupus erythematosus*[5-7] may be due to photosensitivity reactions.

Other reported skin reactions include *vasculitis*,[8,9] *erythema multiforme*,[9] and *pseudoporphyria*.[10]

1. Stone K. Photosensitivity reactions to drugs. *Aust J Pharm* 1985; **66:** 415–18.
2. Addo HA, *et al.* Thiazide-induced photosensitivity: a study of 33 subjects. *Br J Dermatol* 1987; **116:** 749–60.
3. Robinson HN, *et al.* Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985; **121:** 522–4.
4. Graham-Brown R. Lichen planus and lichen-planus-like reactions. *Br J Hosp Med* 1986; **36:** 281–4.
5. Jones SK, *et al.* Thiazide diuretic-induced subacute cutaneous lupus-like syndrome. *Br J Dermatol* 1985; **113** (suppl 29): 25.
6. Reed BR, *et al.* Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 1985; **103:** 49–51.
7. Darken M, McBurney EI. Subacute cutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. *J Am Acad Dermatol* 1988; **18:** 38–42.
8. Björnberg A, Gisslén H. Thiazides: a cause of necrotising vasculitis? *Lancet* 1965; **ii:** 982–3.
9. Hardwick N, Saxe N. Patterns of dermatology referrals in a general hospital. *Br J Dermatol* 1986; **115:** 167–76.
10. Motley RS. Pseudoporphyria due to Dyazide in a patient with vitiligo. *BMJ* 1990; **300:** 1468.

Gout. Thiazides have been associated with hyperuricaemia and gout in some patients. In the Medical Research Council Study on Mild to Moderate Hypertension,[1] a single-blinded trial, men taking bendroflumethiazide had higher incidences of gout than those receiving placebo (12.23 and 1.03 per 1000 patient-years, respectively). The risk appears to be dose-related; in a retrospective study[2] in patients aged 65 or older receiving antihypertensive therapy, there was a significantly increased risk of starting anti-gout therapy in patients taking the equivalent of 25 mg hydrochlorothiazide or more daily, but not in those on lower doses.

1. Greenburg G. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; **ii:** 539–43.
2. Gurwitz JH, *et al.* Thiazide diuretics and the initiation of antigout therapy. *J Clin Epidemiol* 1997; **50:** 953–9.

Withdrawal. For a report of oedema after abrupt withdrawal of thiazides, see under Precautions, below.

Treatment of Adverse Effects

Hypokalaemia in patients treated with thiazides may be avoided or treated by use with potassium or a potassium-sparing diuretic (but see the discussion on potassium supplements, under Effects on Electrolyte Balance in Adverse Effects, above). Hypokalaemia can also be reduced by moderate sodium restriction. With the exception of patients with conditions such as hepatic failure or renal disease, chloride deficiency is usually mild and does not require specific treatment. Apart from the rare occasions when it is life-threatening, dilutional hyponatraemia is best treated with water restriction rather than salt therapy; in true hyponatraemia, appropriate replacement is the treatment of choice (see p.1670).

In massive overdosage, treatment should be symptomatic and directed at fluid and electrolyte replacement. Use of activated charcoal should be considered if the patient presents within 1 hour of ingestion.

Precautions

All diuretics produce changes in fluid and electrolyte balance (see Adverse Effects, above). They should be used with caution in patients with existing fluid and electrolyte disturbances or who are at risk from changes in fluid and electrolyte balance, such as the elderly. They should be avoided in patients with severe hepatic impairment, in whom encephalopathy may be precipitated. Patients with hepatic cirrhosis are also more likely to develop hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses of thiazides and restricted salt intake. All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy. Thiazides should not be given to patients with Addison's disease.

Diuretics should also be given with caution in renal impairment since they can further reduce renal function. Most thiazides are not effective in patients with a creatinine clearance of less than 30 mL/minute. They should not be used in patients with severe renal impairment or anuria.

Thiazides may precipitate attacks of gout in susceptible patients. They may cause hyperglycaemia and aggravate or unmask diabetes mellitus. Blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change. Thiazides can reduce urinary excretion of calcium, sometimes resulting in mild hypercalcaemia; they should not be given to patients with pre-existing hypercalcaemia. There is a possibility that thiazides may exacerbate or activate systemic lupus erythematosus in susceptible patients. For a suggestion that thiazides may increase the risk of developing gallstones, see Effects on the Gallbladder, above.

Thiazides cross the placenta and there have been reports of neonatal jaundice, thrombocytopenia, and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion. Treatment with large doses can inhibit lactation.

Breast feeding. Hydrochlorothiazide has been shown to pass into breast milk. In a woman taking 50 mg hydrochlorothiazide daily, peak milk concentrations were found[1] 5 to 10 hours after a dose and were about 25% of peak blood concentrations. No drug could be detected in the infant's blood, and his serum electrolytes, blood glucose, and blood urea nitrogen were normal. The American Academy of Pediatrics considers[2] that hydrochlorothiazide is usually compatible with breast feeding.

1. Miller ME, *et al.* Hydrochlorothiazide disposition in a mother and her breast-fed infant. *J Pediatr* 1982; **101:** 789–91.
2. 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 06/07/04)

Hyperparathyroidism. Hypertension is a complication of primary hyperparathyroidism but thiazides have often been withheld for fear of exacerbating hypercalcaemia. However, no differences in plasma-calcium concentrations were found in 13 patients given thiazides intermittently for up to 18 months. It was therefore concluded that thiazides are not contra-indicated in such patients.[1] They should, however, be stopped before parathyroid function is tested.

1. Farquhar CW, *et al.* Failure of thiazide diuretics to increase plasma calcium in mild primary hyperparathyroidism. *Postgrad Med J* 1990; **66:** 714–16.

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

Withdrawal. In patients with mild hypertension whose blood pressure is consistently controlled, reduction in dosage or withdrawal of antihypertensive drugs may be possible. Serious oedema occurred in 8 patients with controlled hypertension within 2 weeks of abrupt withdrawal of thiazide diuretics.[1] Thiazides were resumed and gradually tapered without recurrence of oedema.

1. Brandspigel K. Diuretic-withdrawal edema. *N Engl J Med* 1986; **314:** 515.

Interactions

Many of the interactions of hydrochlorothiazide and other thiazides are due to their effects on fluid and electrolyte balance. Diuretic-induced hypokalaemia may enhance the toxicity of digitalis glycosides and may also increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole, terfenadine, halofantrine, pimozide, and sotalol. Thiazides may enhance the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, probably by their hypokalaemic effect. The potassium-depleting effect of diuretics may be enhanced by corticosteroids, corticotropin, beta$_2$ agonists such as salbutamol, carbenoxolone, amphotericin B, or reboxetine.

Diuretics may enhance the effect of other antihypertensives, particularly the first-dose hypotension that occurs with alpha blockers or ACE inhibitors. Orthostatic hypotension associated with diuretics may be enhanced by alcohol, barbiturates, or opioids. The antihypertensive effects of diuretics may be antagonised by drugs that cause fluid retention, such as corticosteroids, NSAIDs, or carbenoxolone; diuretics may enhance the nephrotoxicity of NSAIDs. Thiazides have been reported to diminish the response to pressor amines, such as noradrenaline, but the clinical significance of this effect is uncertain.

Thiazides should not usually be used with lithium since the association may lead to toxic blood concentrations of lithium. Other drugs for which increased toxicity has been reported when given with thiazides include allopurinol and tetracyclines. Thiazides may alter the requirements for hypoglycaemics in diabetic patients.

Antibacterials. Severe hyponatraemia has been reported in patients taking *trimethoprim* with co-amilozide[1] and hydrochlorothiazide.[2]

1. Eastell R, Edmonds CJ. Hyponatraemia associated with trimethoprim and a diuretic. *BMJ* 1984; **289:** 1658–9.
2. Hart TL, *et al.* Hyponatremia secondary to thiazide-trimethoprim interaction. *Can J Hosp Pharm* 1989; **42:** 243–6.

Antiepileptics. There has been a report of symptomatic hyponatraemia associated with the use of hydrochlorothiazide or furosemide and *carbamazepine*.[1]

1. Yassa R, *et al.* Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; **48:** 281–3.

Bile-acid binding resins. Gastrointestinal absorption of both chlorothiazide and hydrochlorothiazide has been reported to be reduced by *colestipol* and *colestyramine*.[1-3] In a study in healthy subjects[2] colestyramine had the greatest effect on hydrochlorothiazide, decreasing absorption by 85% compared with a decrease of 43% with colestipol. Even when colestyramine was given 4 hours after hydrochlorothiazide[3] reductions of absorption of at least 30 to 35% could be expected.

1. Kauffman RE, Azarnoff DL. Effect of colestipol on gastrointestinal absorption of chlorothiazide in man. *Clin Pharmacol Ther* 1973; **14:** 886–90.
2. Hunninghake DB, *et al.* The effect of cholestyramine and colestipol on the absorption of hydrochlorothiazide. *Int J Clin Pharmacol Ther Toxicol* 1982; **20:** 151–4.
3. Hunninghake DB, Hibbard DM. Influence of time intervals for cholestyramine dosing on the absorption of hydrochlorothiazide. *Clin Pharmacol Ther* 1986; **39:** 329–34.

Calcium salts. The milk-alkali syndrome, characterised by hypercalcaemia, metabolic alkalosis, and renal failure, developed in a patient taking chlorothiazide and moderately large doses of calcium carbonate.[1] Patients taking thiazides may be at increased risk of developing the syndrome because of their reduced ability to excrete excess calcium. Hypercalcaemia may also occur in patients taking thiazides with drugs that increase calcium levels, such as vitamin D.

1. Gora ML, *et al.* Milk-alkali syndrome associated with use of chlorothiazide and calcium carbonate. *Clin Pharm* 1989; **8:** 227–9.

Dopaminergics. For a report of increased *amantadine* toxicity associated with hydrochlorothiazide and triamterene, see p.793.

NSAIDs. NSAIDs cause fluid retention and may antagonise the diuretic actions of thiazides.[1]

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Pharmacokinetics

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Beermann B, *et al.* Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin Pharmacol Ther* 1976: **19:** 531–7.
2. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in man. *Eur J Clin Pharmacol* 1977; **12:** 297–303.
3. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in patients with congestive heart failure. *Br J Clin Pharmacol* 1979: **7:** 579–83.

Uses and Administration

Hydrochlorothiazide and the other thiazide diuretics are used in the treatment of hypertension (p.1171), either alone or with other antihypertensives such as ACE inhibitors and beta blockers. They are also used to treat oedema associated with heart failure (p.1165) and with renal and hepatic disorders. Other indications have included the treatment of oedema accompanying the premenstrual syndrome (p.2099), the prevention of water retention associated with corticosteroids and oestrogens, the treatment of diabetes insipidus (below), and the prevention of renal calculus formation in patients with hypercalciuria (below).

Thiazides are moderately potent diuretics and exert their diuretic effect by reducing the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. They act mainly at the beginning of the distal tubules. The excretion of other electrolytes, notably potassium and magnesium, is also increased. The excretion of calcium is reduced. They also reduce carbonic-anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small compared with the effect on chloride excretion and does not appreciably alter the pH of the urine. They may also reduce the glomerular filtration rate.

Their hypotensive effect is probably partly due to a reduction in peripheral resistance; they also enhance the effects of other antihypertensives. Paradoxically, thiazides have an antidiuretic effect in patients with diabetes insipidus.

Administration and dosage. Thiazides are usually given in the morning so that sleep is not interrupted by diuresis. Diuresis starts in about 2 hours after oral doses of hydrochlorothiazide, reaches a maximum in about 4 hours, and lasts for 6 to 12 hours.

The dosage of thiazides should be adjusted to the minimum effective dose. In general lower doses are required for the treatment of hypertension than for oedema, although the maximum therapeutic effect may not be seen for several weeks.

They may be given to patients with mild renal impairment, but thiazides are generally not effective at a creatinine clearance of less than 30 mL/minute.

Hydrochlorothiazide is given orally.

In the treatment of **hypertension** an initial dose of 12.5 mg may be sufficient, increasing to 25 to 50 mg daily if necessary, either alone or with other antihypertensives. Doses of up to 100 mg have been suggested but are rarely necessary.

In the treatment of **oedema** the usual dose is 25 to 100 mg daily, reduced to a dose of 25 to 50 mg daily or intermittently; in severe cases initial doses of up to 200 mg daily have been suggested, but the more powerful loop diuretics (see Furosemide, p.1292) are preferred in such patients.

In the treatment of nephrogenic **diabetes insipidus** an initial dose of up to 100 mg daily may be used.

An initial dose for children has been 1 to 2 mg/kg daily in single or 2 divided doses. Infants under 6 months may need doses of up to 3 mg/kg daily.

For discussion of potassium supplementation in patients taking thiazide diuretics see Effects on Electrolyte Balance, under Adverse Effects, above.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p.1500) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p.1294); results with hydrochlorothiazide or spironolactone have been more ambiguous. No beneficial effects on lung function or oxygenation were found in a study of 12 infants after 1 week of treatment with hydrochlorothiazide and spironolactone.[1] However, hydrochlorothiazide and spironolactone therapy was found to improve total respiratory system compliance with decreased lung damage and increased survival rate in 34 premature infants with bronchopulmonary dysplasia after 8 weeks of therapy.[2] In the latter study furosemide was also given if clinically indicated.

1. Engelhardt B, *et al.* Effect of spironolactone-hydrochlorothiazide on lung function in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1989; **114:** 619–24.
2. Albersheim SG, *et al.* Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989; **115:** 615–20.

Diabetes insipidus. Thiazide diuretics are used in nephrogenic diabetes insipidus (p.2179), sometimes with potassium-sparing diuretics. For instance, hydrochlorothiazide with amiloride was effective in controlling nephrogenic diabetes insipidus in 5 boys and compared favourably with treatment with hydrochlorothiazide and indometacin.[1] Treatment was well tolerated in 4 patients. Abdominal pain and anorexia necessitated withdrawal of amiloride in the fifth patient after 6 months. The use of hydrochlorothiazide with amiloride avoided the need for potassium supplements, which were required with hydrochlorothiazide and indometacin. The use of hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; **117:** 499–502.
2. Kirchlechner V, *et al.* Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; **80:** 548–52.

Hypoparathyroidism. In hypoparathyroidism (p.1087), treatment is usually with oral vitamin D compounds to correct the hypocalcaemia. Thiazides may be useful in some patients. Beneficial effects on serum-calcium concentrations in patients with hypoparathyroidism have been reported after chlortalidone plus dietary salt restriction,[1] and with bendroflumethiazide.[2] However, chlortalidone has not been found to be effective in all patients,[3] and the reduction in urinary calcium excretion by thiazides has been shown to be diminished in patients with hypoparathyroidism,[4] suggesting that this effect may be dependent on the presence of active parathyroid hormone. Care should be taken when giving diuretics to hypoparathyroid patients with co-existing adrenal insufficiency[3] or metabolic alkalosis.[5]

1. Porter RH, *et al.* Treatment of hypoparathyroid patients with chlorthalidone. *N Engl J Med* 1978; **298:** 577–81.
2. Newman GH, *et al.* Effect of bendrofluazide on calcium reabsorption in hypoparathyroidism. *Eur J Clin Pharmacol* 1984; **27:** 41–6.
3. Gertner JM, Genel M. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **298:** 1478.
4. Middler S, *et al.* Thiazide diuretics and calcium metabolism. *Metabolism* 1973; **22:** 139–45.
5. Barzel US. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **289:** 1478.

Ménière's disease. In Ménière's disease (p.564) there is an excess of endolymph fluid in the ear and diuretics such as hydrochlorothiazide have been used in attempts to relieve symptoms by reducing the amount of fluid.

Osteoporosis. Although some epidemiological studies have indicated beneficial effects of thiazides on bone (reduced rates of bone loss[1] and a reduced risk of hip fracture[2-5]) a comprehensive analysis involving 9704 women over the age of 65 years[6] showed only a small effect on bone mass, no effect on the risk for falls, and no overall protective effect against fractures. A further prospective study[7] reported a reduction in forearm fracture, but hip fracture was only reduced in postmenopausal women. Randomised, controlled studies[8,9] have confirmed that hydrochlorothiazide reduces bone loss, but again the effects were small. Thus, thiazides have no established role in the prevention or treatment of osteoporosis (p.1084). They might, however, be useful to reduce hypercalciuria in patients taking glucocorticoids[10] but serum-potassium concentrations should be monitored closely.

1. Wasnich R, *et al.* Effect of thiazide on rates of bone mineral loss: a longitudinal study. *BMJ* 1990; **301:** 1303–5. Correction. *ibid.* 1991; **302:** 218.
2. Ray WA, *et al.* Long-term use of thiazide diuretics and risk of hip fracture. *Lancet* 1989; **i:** 687–90.
3. LaCroix AZ, *et al.* Thiazide diuretic agents and the incidence of hip fracture. *N Engl J Med* 1990; **322:** 286–90.
4. Felson DT, *et al.* Thiazide diuretics and the risk of hip fracture: results from the Framingham Study. *JAMA* 1991; **265:** 370–3.
5. Schoofs MWCJ, *et al.* Thiazide diuretics and the risk for hip fracture. *Ann Intern Med* 2003; **139:** 476–82.
6. Cauley JA, *et al.* Effects of thiazide diuretic therapy on bone mass, fractures, and falls. *Ann Intern Med* 1993; **118:** 666–73.
7. Feskanich D, *et al.* A prospective study of thiazide use and fractures in women. *Osteoporosis Int* 1997; **7:** 79–84.
8. Reid IR, *et al.* Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. *Am J Med* 2000; **109:** 362–70.
9. LaCroix AZ, *et al.* Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133:** 516–26.
10. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; **112:** 352–64.

Renal calculi. A thiazide diuretic may be given to prevent the recurrence of calcium-containing renal calculi (p.2181) in patients with hypercalciuria.[1,2]

1. Pearle MS, *et al.* Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999; **13:** 679–85.
2. Tiselius H-G, *et al.* European Association of Urology. Guidelines on urolithiasis (issued March 2008). Available at: http://www.uroweb.org/fileadmin/count.php?f=fileadmin%2Ftx_eauguidelines%2FUrolithiasis.pdf (accessed 24/07/08)

Preparations

BP 2008: Co-amilozide Oral Solution; Co-amilozide Tablets; Co-triamterzide Tablets; Hydrochlorothiazide Tablets;

USP 31: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Captopril and Hydrochlorothiazide Tablets; Enalapril Maleate and Hydrochlorothiazide Tablets; Fosinopril Sodium and Hydrochlorothiazide Tablets; Hydrochlorothiazide Tablets; Irbesartan and Hydrochlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Propranolol Hydrochloride and Hydrochlorothiazide Extended-release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Reserpine and Hydrochlorothiazide Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets; Spironolactone and Hydrochlorothiazide Tablets; Timolol Maleate and Hydrochlorothiazide Tablets; Triamterene and Hydrochlorothiazide Capsules; Triamterene and Hydrochlorothiazide Tablets; Valsartan and Hydrochlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Diural; Diurex; Tandiur; ***Austral.:*** Dichlotride†; Dithiazide; ***Austria:*** Esidrex; ***Braz.:*** Clorana; Clorizin; Diurepina; Diuretic†; Diuretil; Diurezin; Drenol; Hidroclorana†; Hidroclorozil; Hidrofall†; Hidrolan; Hidromed; Mictrin†; Neo Hidroclor; ***Canad.:*** Apo-Hydro; HydroDiuril†; Novo-Hydrazide; ***Chile:*** Hidroronol; ***Denm.:*** Dichlotride†; ***Fin.:*** Hydrex; ***Fr.:*** Esidrex; ***Ger.:*** Disalunil; diu-melusin; Esidrix; HCT; HCT-Beta; HCT-gamma; HCT-ISIS; HCTad; ***Hong Kong:*** Hydrozide; ***Hung.:*** Hypothiazid; ***India:*** Aquazide; BPzide; Esidrex†; Hydrazide; Selopres; ***Indon.:*** HCT; Lodoz; ***Israel:*** Disothiazide; ***Ital.:*** Esidrex; ***Malaysia:*** Apo-Hydro; Dichlotride†; Hydrozide; ***Mex.:*** Rofucal; ***Norw.:*** Esidrex; ***Pol.:*** Disalunil†; ***Port.:*** Dichlotride†; ***Rus.:*** Hypothiazid (Гипотиазид); ***S.Afr.:*** Hexazide; Ridaq; ***Singapore:*** Apo-Hydro; Di-Ertride†; Hydrozide; ***Spain:*** Acuretic; Esidrex;

Hidrosaluretil; **Swed.:** Esidrex; **Switz.:** Esidrex; **Thai.:** Dichlotride; Diuret-P†; Hychlozide; Hydrozide; **USA:** Esidrix†; HydroDiuril; Microzide; Mictrin; Oretic†; **Venez.:** Di-Eudrin.

Multi-ingredient: Arg.: Accuretic; Adana Plus; Aldazida; Amiloclor†; Atacand-D; Avapro HCT; Carvedil D; Co-Renitec; CoAprovel; Corbis D; Cozaarex D; Dacten D; Defluin Plus; Diovan D; Diovan Triple; Diubeloc†; Diur Pot; Diurex A; Fabotensil D; Fensartan D; Gadopril D; Gliosartan Plus; Gliotenzide; Hidrenox A; Kinfil D; Klosartan D; Loctenk D; Loplac-D; Losacor D; Lotrial D; Maxen D; Micardis Plus; Moducren†; Moduretic; Niten D; Normatensil†; Paxon-D; Plenacor D; Prenomod†; Presi Regul D; Presinor D; Propayerst Plus†; Ren-Ur; Simultan D; Tacardia D; Tencas D; Tenopres D†; Tensopril D; Tiadyl Plus; Tritace-HCT; Vapresan Diur; Vericordin Compuesto; Zestoretic; Ziac; **Austral.:** Accuretic; Amizide; Atacand Plus; Avapro HCT; Hydrene; Karvezide; Micardis Plus; Moduretic; Monoplus; Olmetec Plus; Renitec Plus; Teveten Plus; **Austria:** Accuzide; Acecomb; Acelisino comp; Aceplus; Aldoretic; Amiloral/HCT; Amiloretik; Amilorid comp; Amilostad HCT; Atacand Plus; Beloc comp; Bisocombin; Bisoprolol comp; Bisoprolol-HCT; Bisostad plus; Blopress Plus; Capozide; Captohexal Comp; Captopril Compositum; Captopril-HCT; Co-Acetan; Co-Angiosan; Co-Captopril; Co-Captotyrol†; Co-Dilatrend; Co-Diovan; Co-Enac; Co-Enalapril; Co-Enaran; Co-Enatyrol†; Co-Hypomed; Co-Lisinostad; Co-Mepril; Co-Renitec; Concor Plus; Confit; Corenistad; Cosaar Plus; Darbalan Plus; Deverol mit Thiazid; Dilaplus; Dytide H; Enacostad†; Enalapril Comp; Enalapril/HCT; Fempress Plus; Fosicomb; Hypren plus; Inhibace Plus; Lannapril plus; Lanuretic; Lisihexal comb; Lisinocomp; Lisinopril comp; Loradur; Metoprolol compositum; MicardisPlus; Moducrin; Moduretic; Nanalan Plus; Ramicomp; Ramipharm comb; Renitec Plus; Rivacor Plus; Salodiur; Seloken retard Plus; Supracid; Synerpril; Teveten Plus; Triamteren comp; Triastad HCT; Triloc; Trioral/HCT; Tritazide; Valsartan/HCTZ†; Zestoretic; **Belg.:** Accuretic; Atacand Plus; Belidral†; Co-Amiloride; Co-Bisoprolol; Co-Diovane; Co-Enalapril; Co-Inhibace; Co-Lisinopril; Co-Quinapril; Co-Renitec; CoAprovel; Cozaar Plus; Docspirochlor; Dytenzide; Emcoretic; Fosidel; Kalten†; Kinzalkomb; Lodoz; Loortan Plus; Maxsoten; Merck-Co-Bisoprolol; Merck-Co-Lisinopril; Micardis Plus; Moduretic; Novazyd†; Olmetec Plus; Sectrazide; Selozide; Teveten Plus; Tritazide; Zestoretic; Zok-Zid; **Braz.:** Adelfan-Esidrex†; Aldazida; Amiretic; Aprozide; Aradois H; Atacand HCT; Atens H; Benicar HCT; Biconcor; Capox H; Captotec + HCT†; Co-Enalil; Co-Enaprotec†; Co-Pressoless; Co-Pressotec; Co-Renitec; Corus H; Cotareg†; Diovan HCT; Diurezin-A; Duopril; Ecator H; Enatec F†; Eupressin H; Gliotenzide; Hidropril; Hydromet; Hyzaar; Iguassina; Lisinoretic†; Lisoclor; Lisonotec†; Lonipril-H; Lopril; Lorsar + HCT†; Lotensin H; Malena HCT; Micardis HCT; Moduretic; Monoplus; Naprix D; Neopress; Olmetec HCT; Polol-H; Prinzide; Pritor HCT; Pryltec-H; Selopress; Tenadren; Torlos H; Triatec D; Vascase Plus; Vasopril Plus; Zestoretic; **Canad.:** Accuretic; Aldactazide; Apo-Amilzide; Apo-Methazide; Apo-Triazide; Atacand Plus; Avalide; Diovan HCT; Gen-Amilazide; Hyzaar; Inhibace Plus; Micardis Plus; Moduret; Novamilor; Novo-Spirozine; Novo-Triamzide; Nu-Amilzide; Nu-Triazide; PMS-Dopazide; Prinzide; Teveten Plus; Timolide†; Vaseretic; Viskazide; Zestoretic; **Chile:** Accuretic; Acerdil-D; Aratan D; Bajaten D; Bilaten-D; Blopress D; Blox-D; CoAprovel; Corodin D; Drinamil; Enalten D; Enalten DN; Esalfon-D; Grifopril-D; Hidroronol T; Hiperson-D; Hipoartel H†; Hyzaar; Inhibace Plus; Losapres-D; Lotrial D; Micardis Plus; Monopril Plus; Normaten; Normaten Plus; Sanipresin-D; Simperten-D; Tareg-D; Tonotensil D; Uren; Valaplex-D; Vartalan D; Zestoretic†; Ziac; **Cz.:** Accuzide; Amilorid/HCT; Amprilan H; Apo-Amilzide; Atacand Plus; Captohexal Comp†; Co-Diovan; CoAprovel; Concor Plus†; Enap-H; Enap-HL; Foprin Plus H; Giovax plus H; Hartil-H; Hyzaar†; Inhibace Plus; Karvezide; Kinzalkomb; Limorid†; Lipribela plus H; Lodoz; Loradur; Lorista H; Losaratio Plus H; Lozap H; Medoram plus H; MicardisPlus; Miril plus H; Moduretic; Nopretens Plus H; Olmetec Plus H; PritorPlus; Ramil H; Ramixa Plus H; Rhefluin; Sarten Plus H; Stadapress; Tebis Plus H; Teveten Plus H; Tritazide; **Denm.:** Amilco; AtacandZid; Atazid; Capozid; Co-Renitec†; CoAprovel; Corodil Comp; Cozaar Comp; Diovan Comp; Enacozid; Fortzaar; Kinzalkomb†; Lisinoplus; MicardisPlus; Moduretic†; Sparkal; Synerpril; Teveten Comp; Triatec Comp; Vivazid†; Zestoretic; Zok-Zid; **Fin.:** Accupro Comp; Acercomp†; Amitrid; Atacand Plus; Bisoprolol Comp; Cardace Comp; Cozaar Comp; Diovan Comp; Diuramin; Diurex; Emconcor Comp; Enalapril Comp; Enaloc Comp†; Kinzalkomb; Linatil Comp; Lisipril Comp; MicardisPlus; Miloride; Moduretic; Orloc Comp; Renitec Comp; Renitec Plus; Selocomp ZOC; Sparkal; Teveten Comp; Vivatec Comp; **Fr.:** Aculix; Alteisduo; Briazide; Captea; Cibadrex; Co-Renitec; CoAprovel; Cokenzen; Coolmetec; Cotareg; Coteveten; Cotriatec; Ecazide; Fortzaar; Fozitetic; Hytacand; Hyzaar; Koretic; Lodoz; MicardisPlus; Moducren; Moduretic; Nisisco; Prestole; Prinzide; PritorPlus; Wytens; Zestoretic; Zofenilduo; **Ger.:** Accuzide; ACE-Hemmer comp; Acenorm HCT†; Acercomp; Adelphan-Esidrix†; Adocomp; Amilocomp beta; Amiloretik; Amilorid comp; Amilorid/HCT; Amilozid†; Aquaretic†; Atacand Plus; Azumetop HCT†; Barotonal†; Beloc-Zok comp; Benalapril Plus; Benazeplus; Benazepril comp; Benazepril HCT; Beta-Turfa; Biso comp; Biso-Puren comp; Bisobeta comp; Bisohexal plus; BisoLich comp; Bisomerck Plus; Bisoplus; Bisoprolol Comp; Bisoprolol HCT; Bisoprolol Plus; Blopress Plus; Capozide; Capto Comp; Capto Plus; Captobeta Comp; Captodoc Comp; Captogamma HCT; Captohexal Comp; Captopril Comp; Captopril HCT; Captopril Plus; Cardiagen HCT; Cibadrex; Co-Diovan; CoAprovel; Concor Plus; Cordinate plus; Coric Plus; Corindocomb†; Corvo HCT; Delix Plus; Disalpin†; Diu Venostasin; Diuretikum Verla; Diursan; Diutensat comp†; Diutensat†; Dociteren; duradiuret†; durarese†; Dynacil comp; Dynorm Plus; Dytide H; Emestar plus; Enabeta comp; Enadura Plus; Enahexal comp; Enala-Q comp; Enalagamma HCT; Enalapril Comp; Enalapril HCT; Enalapril plus; Enalapril-saar Plus; EnaLich comp; Enaplus; Esimil†; Fempress Plus; Fondril HCT; Fortzaar; Fosinorm comp; Haemiton compositum†; Isoptin plus; Jenateren comp†; Jutacor comp; Karvezide; Kinzalkomb; Lisi-Puren comp; Lisibeta comp; Lisigamma HCT; LisiLich comp; Lisinopril comp; Lisinopril HCT; Lisiplus; Lisodura plus; Lorzaar plus; Meprolol Comp; Meto comp†; Meto-Isis comp†; meto-thiazid†; Metobeta comp; Metodura comp; Metohexal comp; Metoprolol comp; Metostad Comp; MicardisPlus; Moducrin; Moduretik; Nephral; Olmetec Plus; Pres plus; Propra comp; Provas comp; QuinaLich comp; Quinaplus; Quinapril comp; Rami-Q comp; Ramicard Plus; Ramigamma HCT; RamiLich comp; Ramiplus; Ramipril comp; Ramipril HCT; Ramipril HCTad; Ramipril Plus; Renacor; Risicordin†; Sali-Puren†; Spironothiazid; Tensobon comp; Teveten Plus; Thiazid-comp; Treloc; Tri-Thiazid; Tri-Thiazid Reserpin†; Triampur Compositum; Triamteren comp; Triamteren HCT; Triamteren tri-comp; Triamteren-H†; Triarese; triazid†; Triniton; Turfa; Veratide; Vesdil plus; Votum Plus; **Gr.:** Accuretic; Anastol; Atacand Plus; Bumeftyl; Captopress; Captospes+H; Cibadrex; Co-Dalzad; Co-Diovan; Co-Renitec; CoAprovel; Coredopril; Dosturel; Ekzevit†; Empirol; Fetylan; Fozide; Hydromet†; Hyzaar; Iperton; Ividol; Karvezide; Kifarol; Micardis Plus; Modinexil†; Moduretic; Monoplus†; Nolarmin; Normolose-H; Olartan Plus; Olmetec Plus; Penopril; Pentatec; Piesital; Prinzide; Pritor Plus; Protal complex; Quimea; Return; Sancazid; Savosan; Sedapressin; Siberian; Stibenyl HCT; Superace; Teveten Plus; Tiaden; Triatec Plus; Uresan; Vascase Plus; Z-Bec Plus; Zestoretic; Zidepril; Zofepril Plus; Zopranol Plus; **Hong Kong:** Adelphane-Esidrex; Amilco†; Amithiazide; Apo-Amilzide; Apo-Triazide; Aprovel HCT†; Betaloc Comp; Blopress Plus; Co-Diovan; Co-Renitec; CoAprovel; CP-Metolol Co; Dyazide; Hyzaar; Lodoz; Micardis Plus; Moducren; Moduretic; Sefaretic; Teveten Plus; Triam-Co†; Zestoretic; **Hung.:** Accuzide; Acepril PlusZ; Amilorid Comp; Amilozid-B; Amprilan HD; Amprilan HL; Atacand Plus; Co-Enalapril; Co-Renitec; CoAprovel; Concor Plus; Diovan HCT; Duopril; Ednyt HCT; Ednyt Plus; Enalapril Hexal Plus; Enalapril-HCT; Enap-HL; Hartil HCT; Hyzaar; Inhibace Plus; Lodoz; Lotensin HCT; Meramyl HCT; MicardisPlus; PritorPlus; Ramace Plusz; Ramiwin HCT; Renapril Plus; Renitec Plus; Tritace-HCT; Varexan HCT; **India:** Adelphane-Esidrex; Alsartan-H; Arkamin-H; Beptazine-H; Biduret; Ciplar-H; Cipril-H; Covance-D; EnAce-D; Hipres-D; Invozide; Lisoril-5HT; Lodoz; Losacar-H; Metolar-H; Ramcor H; Ramipres H; Telma-H†; Telpres-H; Xarb-H; Zaart-H; **Indon.:** Blopress Plus; Capozide; Co-Diovan; CoAprovel; Dellasidrex; Irtan Plus; Lorinid; Micardis Plus; Sectrazide; Ser-Ap-Es; Tenazide; Zestoretic; **Irl.:** Accuretic; Amilco†; Atacand Plus; Capozide; Captor-HCT; Carace Plus; Co-Betaloc; Co-Diovan; CoAprovel; Cozaar Comp; Dyazide; Half Capozide; Innozide; Lispril-hydrochlorothiazide; MicardisPlus; Moducren; Moduret; Teveten Plus; Zesger Plus; Zestoretic; **Israel:** Atacand Plus; Co-Diovan; Irban Plus†; Kaluril; Naprizide; Ocsaar Plus; Tritace Comp; Vascace Plus; Vasopril Plus†; **Ital.:** Accuretic; Acediur; Aceplus; Acequide; Acesistem; Aldactazide; Bifrizide; Blopresid; Cibadrex; CoAprovel; Combisartan; Condiuren; Corixil; Cotareg; Elidiur; Enulid; Femipres Plus; Forzaar; Fosicombi; Gentipress; Hizaar; Idroquark; Inibace Plus; Initiss Plus; Karvezide; Lodoz; Losazid; Medozide; Micardis Plus; Moduretic; Nalapres; Neo-Lotan Plus; Neoprex; Prinzide; PritorPlus; Quinazide; Ratacand Plus; Selozide†; Sinertec; Spiridazide; Tensadiur; Tensozide; Triatec HCT; Uniprildiur; Vasoretic; Zantipride; Zestoretic; Zinadiur; Zopradide; **Malaysia:** Ami-Hydrotride; Amizide; Apo-Amilzide; Apo-Triazide†; Atacand Plus; Co-Diovan; CoAprovel; Fortzaar; Hyzaar; Micardis Plus; Moduretic; Olmetec Plus; **Mex.:** Atacand Plus; Avalide; Biconcor; Blopress Plus; Capozide; Co-Captral; Co-Diovan; Co-Renitec; CoAprovel; Dyazide; Gliotenzide; Hyzaar; Micardis Plus; Moduretic; Predxal Plus; Prinzide; Selopres; Tritazide; Zestoretic; **Neth.:** Acuzide; Atacand Plus; Blopresid; Capozide†; Cibadrex; Co-Diovan; Co-Renitec; Co-Aprovel; Cotareg; Cozaar Plus; Delitab-HCT; Diurace; Dytenzide; Emcoretic; Enacostad†; Fortzaar; Hyzaar; Karvezide; Kinzalkomb; Lisidigal HCT; Losazid; Micardis Plus; Moduretic; Novazyd; Prilitab-HCT; Prilitaril-HCT; PritorPlus; Ramitab-HCT; Rataril-HCT; Renitec Plus; Secadrex†; Selokomb; Teveten Plus; Tritazide; Zestoretic; **Norw.:** Atacand Plus; CoAprovel; Cozaar Comp; Diovan Comp; Enalapril Comp; Lodoz; MicardisPlus; Moduretic; Normorix; Renitec Comp; Teveten Comp; Vivatec Comp; Zestoretic; **NZ:** Accuretic; Amizide; Capozide; Co-Renitec; Hyzaar; Inhibace Plus; Karvezide; Triamizide; **Philipp.:** Accuzide; Betazide; Blopress Plus; Co-Diovan; Co-Renitec; CoAprovel; Combizar; Hyzaar; Micardis Plus; Norplus; PritorPlus; Teveten Plus; Uniretic; Vascace Plus; Vascoride; Zestoretic; Ziac; **Pol.:** Accuzide; Co-Diovan; Enap H; Enap HL; Hyzaar; Inhibace Plus; Lorista H; Lotensin HCT; Micardis Plus; Pritor Plus; Ramicor Comb; Tialorid; **Port.:** Acuretic; Aldoretic†; Amiloride Composto†; Blopress 16 mg + 12,5 mg; Blopress Comp; Chibretico†; Co-Diovan; Co-Tareg; CoAprovel; Concor Plus; Cozaar Plus; Diurene; Dyazide; Ecamais; Enatia; Fortzaar; Fositen Plus; Hytacand; Inibace Plus; Karvezide; Kinzalkomb; Laprilen; Lisoplus; Lopiretic; Lortaan Plus; Medinor; Micardis Plus; Moducren†; Moduretic; Neodur; Normotil†; Norpramin; Olsar Plus; Ondolen; Prinzide; PritorPlus; Ramicor D; Renidur; Renipril Plus; Siaara; Tensival; Teveten Plus; Tiazinol; Triam Tiazida R; Triatec Composto; Vascase Plus; Zestoretic; Zofenil Plus; **Rus.:** Adelphane-Esidrex (Адельфан-эзидрекс); Apo-Triazide (Апо-триазид); Capozide (Капозид); Co-Diovan (Ко-Диован); Co-Renitec (Ко-Ренитек); Enap-H (Энап Н); Enap-HL (Энап-НЛ); Fosicard H (Фозикард Н); Fozide (Фозид); Hyzaar (Гизаар); Iruzid (Ирузид); Lisoretic (Лизоретик); Lozap Plus (Лозап Плюс); MicardisPlus (МикардисПлюс); Moex Plus (Моэкс Плюс); Renipril HT (Рениприл ГТ); Sinorezid (Синорезид); Teveten Plus (Теветен Плюс); Triam-Co (Триам-ко); Triampur Compositum (Триампур Композитум); Triresid K (Тризид К); **S.Afr.:** Accuretic; Adco-Retic; Amiloretic; Atacand Plus; Betaretic; Capozide; Captoretic; Cibadrex; Co-Diovan; Co-Micardis; Co-Renitec; CoAprovel; Cozaar Comp; Dyazide; Enap-Co; Fortzaar; Hexaretic; Inhibace Plus; Lisoretic; Moducren; Moduretic; Monozide; Pharmapress Co; Renezide; Servatrin; Sotazide; Urirex-K; Zapto Co; Zestoretic; Zetomax Co; Ziak; **Singapore:** Apo-Amilzide; Apo-Triazide; Atacand Plus; Co-Diovan; Co-Renitec; CoAprovel; Enap-HL; Gliotenzide; Hyzaar; Lodoz; Micardis Plus; Olmetec Plus; **Spain:** Acediur; Acetensil Plus; Adelfan-Esidrex†; Alopresin Diu†; Ameride; Atacand Plus; Baripril Diu; Bicetil; Bitensil Diu; Cesplon Plus; Cibadrex; Co-Diovan; Co-Renitec; Co-Vals; CoAprovel; Cozaar Plus; Crinoretic; Dabonal Plus; Decresco†; Dilabar Diu; Ditenside; Diuzine; Doneka Plus; Ecadiu; Ecazide; Emcoretic; Fortzaar; Fositens Plus; Futuran Plus; Hiperlex Plus; Hipoartel Plus; Inhibace Plus; Inocar Plus; Iricil Plus; Kalpress Plus; Kalten; Karvezide; Labodrex; Lidaltrin Diu; Micardis Plus; Miscidon†; Miten Plus; Navixen Plus; Neotensin Diu; Parapres Plus; Pressitan Plus; Prinivil Plus; Pritor Plus; Regulaten Plus; Renitecmax; Rulun; Secadrex†; Secubar Diu; Selopresin†; Tensikey Complex; Tensiocomplet; Tenso Stop Plus; Tevetens Plus; Zestoretic; **Swed.:** Accupro Comp; Amiloferm; Atacand Plus; CoAprovel; Cozaar Comp; Diovan Comp; Enalapril Comp; Inhibace comp; Kinzalkomb†; Linatil Comp; Micardis Plus; Moduretic; Monopril comp†; Normorix; Renitec Comp; Sparkal; Synerpril; Teveten Comp; Triatec Comp; Zestoretic; **Switz.:** Accuretic; Adelphan-Esidrex; Agorex†; Amilo-basan†; Amiloride/HCTZ; Atacand Plus; Betadiur†; Blopress Plus; Capozide; Captosol comp; Cibadrex; Co-Acepril; Co-Amilorid†; Co-Diovan; Co-Enalapril; Co-Enatec; Co-Epril; Co-Lisinopril; Co-Reniten; Co-Vasocor; CoAprovel; Comilorid; Concor Plus; Corprimetic; Cosaar Plus; Dyazide; Ecodurex; Elpradil HCT; Epril Plus; Escoretic; Fosicomp; Grodurex; Inhibace Plus; Kalten; Kinzalplus; Lisitril comp; Lisopril plus; Lodoz; MicardisPlus; Moducren; Moduretic; Olmetec Plus; Prinzide; Provas comp; Provas maxx; Reniten Plus; Rhefluin; t/h-basan; Tensobon comp; Teveten Plus; Tobicor Plus; Triatec Comp; Votum Plus; Zestoretic; **Thai.:** Aprovel HCT†; Bilduretic; Blopress Plus; Co-Diovan; CoAprovel; Dazid†; Dinazide; Dyazide; Dyterene†; Fortzaar; Hydrares; Hydrozide Plus; Hyperretic; Hypery†; Hyzaar; Lodoz; Mano-Ap-Es; Medeserpine Co†; Micardis Plus; Miduret†; Milorex†; Miretic; Modulan†; Moduretic; Monoplus; Moure-M; Poli-Uretic; Renase; Reser; Sefaretic; Ser-Ap-Es; **Turk.:** Accuzide; Adelphan-Esidrex; Aldactazide; Atacand Plus; Cibadrex; Co-Diovan; Delix Plus; Eklips Plus; Hyzaar; Inhibace Plus; Karvezide; Konveril Plus; Micardis Plus; Moduretic; Monopril Plus; Pritor Plus; Rilace Plus; Sinoretik; Triamteril; Zestoretic; **UK:** Accuretic; Acezide; Amil-Co; Capozide; Capto-Co; Carace Plus; Caralpha; Co-Betaloc†; Co-Diovan; Co-Aprovel; Cozaar Comp; Dyazide; Innozide; Kalten; Lisicostad; MicardisPlus; Moducren†; Moduret; Moduretic; Olmetec Plus; Secadrex†; Triamaxco†; Triamco; Zestoretic; **USA:** Accuretic; Aldactazide; Aldoril†; Apresazide†; Atacand HCT; Avalide; Benicar HCT; Candepressin Plus; Capozide; Diovan HCT; Dyazide; Esimil; Hydra-zide; Hydrap-ES†; Hydro-Serp†; Hydropres; Hydroserpine†; Hyzaar; Inderide†; Lopressor HCT; Lotensin HCT; Marpres; Maxzide; Micardis HCT; Moduretic; Monopril-HCT; Prinzide; Quinaretic; Ser-Ap-Es†; Teveten HCT; Timolide; Tri-Hydroserpine†; Uniretic; Vaseretic; Zestoretic; Ziac; **Venez.:** Accuretic; Aldactazida; Altace Plus; Atacand Plus; Biconcor; Blopress Plus; Capozide; Cartazid†; Co-Renitec; Co-Aprovel; Cormatic; Diovan HCT; Hyzaar Plus; Lisiletic; Micardis Plus; Moduretic; Monopril Plus; Nefrotal H; Priretic†; Pritor Plus; Quinaretic; Reminalet; Vasaten HCT; Ziac.

Hydroflumethiazide *(BAN, rINN)* ⊗

Hidroflumetiazida; Hydrofluméthiazide; Hydroflumethiazidum; Hydroflumetiatsidi; Hydroflumetiazid; Trifluoromethylhydrothiazide. 3,4-Dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

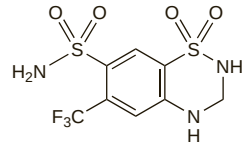
Гидрофлуметиазид

$C_8H_8F_3N_3O_4S_2$ = 331.3.

CAS — 135-09-1.

ATC — C03AA02.

ATC Vet — QC03AA02.



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

- Co-flumactone (*BAN*)—hydroflumethiazide and spironolactone in equal parts (w/w).

Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Hydroflumethiazide). White or almost white, odourless or almost odourless, glistening crystals or crystalline powder. Practically insoluble in water; soluble in alcohol; practically insoluble in chloroform and in ether.

USP 31 (Hydroflumethiazide). A white to cream-coloured, odourless, finely divided crystalline powder. Very slightly soluble in water and in chloroform; soluble 1 in 39 of alcohol and 1 in 2500 of ether; freely soluble in acetone. A 1% dispersion in water has a pH of 4.5 to 7.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Hydroflumethiazide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a beta-phase biological half-life of about 17 hours and a metabolite with a longer half-life that is extensively bound to red blood cells. Hydroflumethiazide is excreted in the urine; its metabolite has also been detected in the urine.

◊ References.

1. Brørs O, *et al*. Pharmacokinetics of a single dose of hydroflumethiazide in health and in cardiac failure. *Eur J Clin Pharmacol* 1978; **14:** 29–37.

Uses and Administration

Hydroflumethiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p.1310). It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis begins about 2 hours after an oral dose and has been reported to last for up to 24 hours.

In the treatment of **oedema** the usual initial dose is 50 to 100 mg daily, in one or two divided doses, reduced to a dose of 25 to 50 mg on alternate days or intermittently. Doses of up to 200 mg daily may be required by some patients. In the treatment of **hypertension** the usual dose is 25 to 50 mg daily either alone, or with other antihypertensives. An initial dose of 12.5 mg has been used.

An initial dose for children is 1 mg/kg daily, reduced for maintenance.

Preparations

BP 2008: Hydroflumethiazide Tablets;
USP 31: Hydroflumethiazide Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Diucardin†; Saluron.

Multi-ingredient: ***Irl.:*** Adactide; ***S.Afr.:*** Protensin-M; ***UK:*** Aldactide; ***USA:*** Salutensin†.