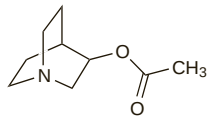
Aceclidine *(USAN, rINN)*

Aceclidina; Acéclidine; Aceclidinum. 1-Azabicyclo[2.2.2]octan-3-ol acetate; 3-Quinuclidinol acetate; 3-Acetoxyquinuclidine.

Ацеклидин

$C_9H_{15}NO_2$ = 169.2.
CAS — 827-61-2.
ATC — S01EB08.
ATC Vet — QS01EB08.



Aceclidine Hydrochloride *(rINNM)*

Acéclidine, Chlorhydrate d'; Aceclidini Hydrochloridum; Hidrocloruro de aceclidina.

Ацеклидина Гидрохлорид

$C_9H_{15}NO_2$,HCl = 205.7.
CAS — 6109-70-2.
ATC — S01EB08.
ATC Vet — QS01EB08.

Profile

Aceclidine hydrochloride is a parasympathomimetic miotic (see Pilocarpine, p.1884) that is a cholinergic agonist. It has been used in eye drops to lower intra-ocular pressure in patients with glaucoma.

Use. Aceclidine has been tried for the management of disturbances of night vision after laser refractive surgery.[1]

1. Randazzo A, *et al*. Pharmacological management of night vision disturbances after refractive surgery: results of a randomized clinical trial. *J Cataract Refract Surg* 2005; **31:** 1764–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Glaucostat†; Glaunorm; ***Ital.:*** Glaunorm; ***Neth.:*** Glaucocare†; ***Port.:*** Glaucostat†.

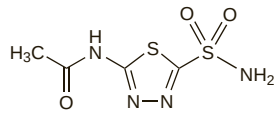
Multi-ingredient: ***Ital.:*** Glautimol.

Acetazolamide *(BAN, rINN)* ⊗

Acetazolam; Acetazolamid; Acetazolamida; Acetazolamidas; Acétazolamide; Acetazolamidum; Asetatsoliamidi; Asetazolamid. 5-Acetamido-1,3,4-thiadiazole-2-sulphonamide; *N*-(5-Sulphamoyl-1,3,4-thiadiazol-2-yl)acetamide.

Ацетазоламид

$C_4H_6N_4O_3S_2$ = 222.2.
CAS — 59-66-5.
ATC — S01EC01.
ATC Vet — QS01EC01.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*
Ph. Eur. 6.2 (Acetazolamide). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.
USP 31 (Acetazolamide). A white to faintly yellowish-white, odourless, crystalline powder. Very slightly soluble in water; sparingly soluble in practically boiling water; slightly soluble in alcohol. Store in airtight containers.

Acetazolamide Sodium *(BANM, rINNM)* ⊗

Acetazolamida sódica; Acétazolamide Sodique; Natrii Acetazolamidum; Sodium Acetazolamide.

Натрий Ацетазоламид

$C_4H_5N_4NaO_3S_2$ = 244.2.
CAS — 1424-27-7.
ATC — S01EC01.
ATC Vet — QS01EC01.

Stability. Solutions of acetazolamide sodium in glucose 5% and sodium chloride 0.9% were stable for 5 days at 25° with a loss of potency of less than 7.2%.[1] At 5° the loss of potency in both solutions was less than 6% after 44 days of storage. Small reductions in pH were recorded, possibly due to the formation of acetic acid during the decomposition of acetazolamide. At –10° the loss in potency after 44 days of storage was less than 3% in both solutions. Results were similar in samples thawed in tap water and in a microwave oven.

An oral suspension of acetazolamide 25 mg/mL prepared from tablets with the aid of sorbitol solution 70% was stable for at least 79 days at 5°, 22°, and 30°. It was recommended that the formulation be maintained at pH 4 to 5 and stored in amber glass bottles.[2]

1. Parasrampuria J, *et al*. Stability of acetazolamide sodium in 5% dextrose or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1987; **44:** 358–60.
2. Alexander KS, *et al.* Stability of acetazolamide in suspension compounded from tablets. *Am J Hosp Pharm* 1991; **48:** 1241–4.

Adverse Effects

Common adverse effects of acetazolamide are malaise, fatigue, depression, excitement, headache, weight loss, and gastrointestinal disturbances. Drowsiness and paraesthesia involving numbness and tingling of the face and extremities are also common with high doses in particular. Diuresis can be troublesome, but generally abates after a few days of continuous therapy. Acidosis may develop during treatment and is generally mild but severe metabolic acidosis has occasionally been reported, especially in elderly or diabetic patients or those with renal impairment. Electrolyte imbalances including hyponatraemia and hypokalaemia may occasionally occur; hypokalaemia is generally transient and rarely clinically significant.

Blood dyscrasias occur rarely and may include aplastic anaemia, agranulocytosis, leucopenia, thrombocytopenia, and thrombocytopenic purpura. Acetazolamide can give rise to crystalluria, renal calculi, and renal colic; renal lesions, possibly due to a hypersensitivity reaction, have also been reported.

Other adverse reactions include allergic skin reactions, fever, thirst, dizziness, ataxia, irritability, confusion, reduced libido, haematuria, glycosuria, renal failure, abnormal liver function tests, loss of appetite, alterations in taste, transient myopia, and tinnitus and hearing disturbances. Rare reactions include photosensitivity, hepatitis or cholestatic jaundice, flaccid paralysis, and convulsions.

Intramuscular injections are painful owing to the alkalinity of the solution.

Effects on the blood. Severe, often fatal, blood dyscrasias have been reported in patients taking acetazolamide. By 1989, the National Registry of Drug-Induced Ocular Side Effects in the USA[1] had received reports of haematological reactions possibly due to carbonic anhydrase inhibitors in 139 patients, of which 50 cases (36%) were fatal. Most deaths were due to aplastic anaemia. Over half the reactions occurred during the first 6 months of therapy. The value of periodic blood analysis in patients taking carbonic anhydrase inhibitors for prolonged periods has been debated[2-7] but is advised by licensed product information. The US National Registry has recommended[8] that initial and 6-monthly blood analysis should be undertaken.

1. Fraunfelder FT, Bagby GC. Possible hematologic reactions associated with carbonic anhydrase inhibitors. *JAMA* 1989; **261:** 2257.
2. Alm A, *et al.* Monitoring acetazolamide treatment. *Acta Ophthalmol (Copenh)* 1982; **60:** 24–34.
3. Johnson T, Kass MA. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1986; **101:** 128–9.
4. Zimran A, Beutler E. Can the risk of acetazolamide-induced aplastic anemia be decreased by periodic monitoring of blood cell counts? *Am J Ophthalmol* 1987; **104:** 654–8.
5. Lichter PR. Carbonic anhydrase inhibitors, blood dyscrasias, and standard-of-care. *Ophthalmology* 1988; **95:** 711–12.
6. Mogk LG, Cyrlin MN. Blood dyscrasias and carbonic anhydrase inhibitors. *Ophthalmology* 1988; **95:** 768–71.
7. Miller RD. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 745–6.
8. Fraunfelder FT, *et al*. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 79–81.

Effects on electrolyte balance. Acetazolamide has been reported to cause symptomatic metabolic acidosis in the elderly, in diabetic patients, and in those with renal impairment.[1-6] Raised plasma-acetazolamide concentrations have been reported in elderly patients, probably attributable to reduced renal function, and in 6 of 9 glaucoma patients this was associated with hyperchloraemic metabolic acidosis.[7] A single-dose study[8] in 4 elderly patients found that reduced acetazolamide clearance correlated with renal function. Urea and electrolyte concentrations should be measured before and during treatment with acetazolamide, particularly in the elderly and in other patients, such as diabetics, who may have renal impairment.

1. Maisey DN, Brown RD. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1981; **283:** 1527–8.
2. Goodfield M, *et al.* Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; **284:** 422.
3. Reid W, Harrower ADB. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; **284:** 1114.
4. Heller I, *et al.* Significant metabolic acidosis induced by acetazolamide: not a rare complication. *Arch Intern Med* 1985; **145:** 1815–17.
5. Parker WA, Atkinson B. Acetazolamide therapy and acid-base disturbance. *Can J Hosp Pharm* 1987; **40:** 31–4.
6. Zaidi FH, Kinnear PE. Acetazolamide, alternate carbonic anhydrase inhibitors and hypoglycaemic agents: comparing enzymatic with diuresis induced metabolic acidosis following intraocular surgery in diabetes. *Br J Ophthalmol* 2004; **88:** 714–15.
7. Chapron DJ, *et al.* Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; **29:** 348–53.
8. Chapron DJ, *et al.* Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; **19:** 363–71.

Effects on endocrine function. Hirsutism occurred in a 2½-year-old girl after treatment for 16 months with acetazolamide for congenital glaucoma.[1] There was no evidence of virilisation.

1. Weiss IS. Hirsutism after chronic administration of acetazolamide. *Am J Ophthalmol* 1974; **78:** 327–8.

Effects on the kidneys. Large reductions in glomerular filtration rate occurred during treatment with carbonic anhydrase inhibitors in 3 type 1 diabetics with nephropathy and glaucoma.[1] Kidney function improved when the drug was withdrawn.

1. Skøtt P, *et al*. Effect of carbonic anhydrase inhibitors on glomerular filtration rate in diabetic nephropathy. *BMJ* 1987; **294:** 549.

Effects on the liver. For a report of liver damage associated with use of acetazolamide, see Hypersensitivity, below.

Effects on the skin. Rashes, including severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported during acetazolamide therapy; the fact that acetazolamide is a sulfonamide-derivative has been suggested as a cause for these reactions. Photosensitivity has also been noted rarely.

Severe exacerbation of rosacea occurred in a patient taking acetazolamide for glaucoma; the rosacea improved on withdrawal of acetazolamide and relapsed again on its reintroduction.[1]

1. Shah P, *et al.* Severe exacerbation of rosacea by oral acetazolamide. *Br J Dermatol* 1993; **129:** 647–8.

Extravasation. Extravasation was reported in a patient after intravenous acetazolamide and led to severe ulceration requiring surgery to repair the skin defect.[1] It was recommended that 1 to 2 mL of sodium citrate 3.8% should be injected subcutaneously near the site of extravasation in order to neutralise the alkaline effects of the acetazolamide injection.

1. Callear A, Kirkby G. Extravasation of acetazolamide. *Br J Ophthalmol* 1994; **78:** 731.

Hypersensitivity. A 54-year-old man with glaucoma who was treated with acetazolamide 500 mg daily for 26 days developed a generalised erythematous rash and became delirious, dehydrated, markedly jaundiced, with peripheral circulatory failure, and died from cholestatic jaundice with hepatic coma and anuria.[1] Drug-induced hypersensitivity and hepatitis due to acetazolamide was suspected.

Anaphylaxis has also been reported[2] after a single oral dose in a patient who had not previously received acetazolamide. However, the patient was hypersensitive to sulfonamides and the reaction may have been caused by cross-sensitivity.

1. Kristinsson A. Fatal reaction to acetazolamide. *Br J Ophthalmol* 1967; **51:** 348–9.
2. Tzanakis N, *et al.* Anaphylactic shock after a single oral intake of acetazolamide. *Br J Ophthalmol* 1998; **82:** 588.

Precautions

Acetazolamide is contra-indicated in the presence of sodium or potassium depletion, in hyperchloraemic acidosis, in conditions such as Addison's disease and adrenocortical insufficiency, and in marked hepatic or renal impairment. Encephalopathy may be precipitated in patients with hepatic dysfunction. It should not be used in chronic angle-closure glaucoma since it may mask deterioration of the condition. Since acetazolamide is a sulfonamide derivative, it should not be used in patients with a history of sulfonamide hypersensitivity.

Acetazolamide should be given with care to patients likely to develop acidosis or with diabetes mellitus; severe metabolic acidosis may occur in the elderly, and in patients with renal impairment, pulmonary obstruction, or emphysema. Acetazolamide may increase the risk of hyperglycaemia in diabetic patients.

Periodic monitoring of plasma electrolytes and blood count is recommended during long-term therapy and patients should be cautioned to report any unusual skin rashes. Acetazolamide is teratogenic in *animals*.

Some adverse effects such as drowsiness and myopia may affect a patient's ability to perform skilled tasks including driving.

Breast feeding. Acetazolamide has been detected in breast milk.[1] However, there have been no reports of adverse effects in breast-fed infants whose mothers were receiving acetazolamide

and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Söderman P, *et al*. Acetazolamide excretion into human breast milk. *Br J Clin Pharmacol* 1984; **17:** 599–600.
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 17/03/06)

Diabetes mellitus. For a brief discussion of metabolic acidosis in patients with diabetes, see Effects on Electrolyte Balance, above.

For a report of deterioration in renal function in patients with diabetic nephropathy who were given carbonic anhydrase inhibitors, see Effects on the Kidneys, above.

The elderly. A retrospective review[1] of 222 patients with glaucoma indicated that those aged 40 years or less tolerated treatment with carbonic anhydrase inhibitors much better than older patients. A single-dose study[2] of acetazolamide in 4 elderly subjects indicated that the capacity to clear acetazolamide from plasma correlated with creatinine clearance and was thus reduced in the elderly. They also had reduced plasma protein binding and the combination of these factors predisposed the elderly to enhanced accumulation of acetazolamide in erythrocytes.

Plasma-acetazolamide concentrations exceeded the **therapeutic range** (5 to 10 micrograms/mL) in 9 of 12 elderly patients receiving acetazolamide for glaucoma or metabolic alkalosis.[3] Hyperchloraemic metabolic acidosis was detected in 6 of 9 glaucoma patients. The excessive plasma concentrations were attributed to age-related reductions in renal function. It was suggested that elderly patients may require reduced doses of acetazolamide.

For reports of symptomatic metabolic acidosis associated with use of acetazolamide in the elderly, see Effects on Electrolyte Balance, above.

1. Shrader CE, *et al*. Relationship of patient age and tolerance to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1983; **96:** 730–3.
2. Chapron DJ, *et al*. Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; **19:** 363–71.
3. Chapron DJ, *et al*. Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; **29:** 348–53.

Interference with laboratory estimations. Acetazolamide interfered with an HPLC method of assay for theophylline[1] resulting in an unnecessary dose reduction and worsening apnoea in an infant. Other workers[2] pointed out that the interference depended on the solvent used in the extraction, and presented evidence to suggest that acetazolamide may not interfere with other assay methods for theophylline.

1. Mecrow IK, Goldie BP. Acetazolamide interferes with theophylline assay. *Lancet* 1987; **i:** 558.
2. Kelsey HC, *et al*. Interference by acetazolamide in theophylline assay depends on the method. *Lancet* 1987; **ii:** 403.

Renal impairment. For a brief discussion of metabolic acidosis in patients with renal impairment, see Effects on Electrolyte Balance, above.

Interactions

By rendering the urine alkaline acetazolamide reduces the urinary excretion, and so may enhance the effects, of drugs such as amfetamines, ephedrine, and quinidine; conversely, urinary alkalinisation can reduce the effects of methenamine and its compounds. Acetazolamide may enhance antiepileptic-induced osteomalacia. Use of acetazolamide with aspirin may result in severe acidosis and increase CNS toxicity. Acetazolamide may affect fluid and electrolyte balance leading to interactions similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309). Unlike thiazides, however, acetazolamide may increase the excretion of lithium.

Antacids. *Sodium bicarbonate* therapy enhances the risk of renal calculus formation in patients taking acetazolamide.[1]

1. Rubenstein MA, Bucy JG. Acetazolamide-induced renal calculi. *J Urol (Baltimore)* 1975; **114:** 610–12.

Antiepileptics. For severe osteomalacia in patients taking acetazolamide with *phenytoin* and other antiepileptics, see Diuretics, p.499. Acetazolamide may increase serum concentrations of *carbamazepine*, see Diuretics, p.475.

Antineoplastics. Alkalinisation of the urine by acetazolamide increases the solubility of *methotrexate* in the urine and also increases its excretion. This effect has been exploited therapeutically to reduce the nephrotoxicity of methotrexate (see Effects on the Kidneys, p.746).

Benzodiazepines. Ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of *triazolam* by acetazolamide.[1]

1. Masuyama S, *et al*. 'Ondine's Curse': side effect of acetazolamide? *Am J Med* 1989; **86:** 637.

Local anaesthetics. For the effect of acetazolamide on *procaine*, see p.1869.

Salicylates. Salicylates displace acetazolamide from plasma protein binding sites and reduce its renal clearance,[1] leading to elevated plasma-acetazolamide concentrations. In addition acidosis produced by acetazolamide may increase salicylate toxicity by enhancing salicylate tissue penetration.[2] Severe metabolic acidosis has been reported[3] in patients with normal renal function given acetazolamide with salicylates.

Use of salicylates with acetazolamide should be avoided if possible, particularly if renal dysfunction is present. If the combination is used, patients should be carefully monitored for symptoms of CNS toxicity such as lethargy, confusion, somnolence, tinnitus, and anorexia.

1. Sweeney KR, *et al*. Toxic interaction between acetazolamide and salicylate: case report and a pharmacokinetic explanation. *Clin Pharmacol Ther* 1986; **40:** 518–24.
2. Anderson CJ, *et al*. Toxicity of combined therapy with carbonic anhydrase inhibitors and aspirin. *Am J Ophthalmol* 1978; **86:** 516–19.
3. Cowan RA, *et al*. Metabolic acidosis induced by carbonic anhydrase inhibitors and salicylates in patients with normal renal function. *BMJ* 1984; **289:** 347–8.

Pharmacokinetics

Acetazolamide is fairly rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 2 hours after oral doses. It has been estimated to have a plasma half-life of about 3 to 6 hours. It is tightly bound to carbonic anhydrase and high concentrations are present in tissues containing this enzyme, particularly red blood cells and the renal cortex; it is highly bound to plasma proteins. It is excreted unchanged in the urine and has been detected in breast milk.

◊ References.

1. Lehmann B, *et al*. The pharmacokinetics of acetazolamide in relation to its use in the treatment of glaucoma and to its effects as an inhibitor of carbonic anhydrases. *Adv Biosci* 1969; **5:** 197–217.

Uses and Administration

Acetazolamide is an inhibitor of carbonic anhydrase with weak diuretic activity and is used mainly in the management of glaucoma. Other indications include epilepsy and high-altitude disorders.

By inhibiting carbonic anhydrase in the eye acetazolamide decreases the formation of aqueous humour and so decreases intra-ocular pressure. It is used in the preoperative management of angle-closure **glaucoma**, or as an adjunct in the treatment of open-angle glaucoma. In the treatment of glaucoma the usual oral dose is 250 to 1000 mg daily; divided doses should be used for amounts greater than 250 mg daily. Modified-release preparations are also available. Although not licensed for children in the UK, the *BNFC* suggests that those aged 1 month to 12 years may be given acetazolamide in oral doses of 10 to 20 mg/kg daily, to a maximum of 750 mg daily, in 2 to 4 divided doses.

Acetazolamide is also used, either alone or with other antiepileptics, for the treatment of various forms of **epilepsy** in oral doses of 250 to 1000 mg daily in divided doses. Licensed product information in the UK suggests an oral dose for children of 8 to 30 mg/kg daily. The *BNFC* recommends an initial oral dose of 2.5 mg/kg 2 or 3 times daily in neonates and children up to 12 years of age; this may then be increased to a maintenance dose of 5 to 7 mg/kg 2 or 3 times daily. The total daily dose for children should not exceed 750 mg.

When oral dosing is impracticable, acetazolamide may be given parenterally as the sodium salt; acetazolamide sodium 275 mg is equivalent to about 250 mg of acetazolamide. It may be given by intramuscular injection but the intravenous route is preferred due to the alkalinity of the solution. Doses are similar to those given orally.

Acetazolamide is also used to prevent or ameliorate the symptoms of **high-altitude disorders**. Prompt descent will still be necessary if severe symptoms such as cerebral oedema or pulmonary oedema occur. The usual oral dose is 500 to 1000 mg daily in divided doses. It may also be given as a modified-release preparation.

Acetazolamide also increases the excretion of bicarbonate and of cations, chiefly sodium and potassium, by inhibiting the reaction catalysed by carbonic anhydrase in the renal tubules, and so promotes an alkaline diuresis. When given orally as an immediate-release preparation, its effect begins within 60 to 90 minutes and lasts for 8 to 12 hours. However, continuous use is associated with metabolic acidosis and an accompanying loss of diuretic activity. Therefore, although acetazolamide has been used as a diuretic, it has largely been superseded by drugs such as the thiazides or furosemide. For **diuresis** the usual oral dose is 250 to 375 mg and is given either once daily or on alternate days; intermittent therapy is required for a continued effect.

Administration in the elderly. For the suggestion that reduced doses may be required in elderly patients see under Precautions, above.

Epilepsy. Acetazolamide may be used in the treatment of epilepsy (p.465) as an alternative or adjunct to first-line drugs for refractory partial seizures with or without secondary generalisation. It is also effective in a number of other refractory forms of epilepsy including atypical absence, tonic, atonic, myoclonic, and menstruation-related seizures (catamenial epilepsy).[1-5] It is believed to act by inhibition of carbonic anhydrase in glial cells in the CNS.[6] The major drawback to the chronic use of acetazolamide is the rapid development of tolerance,[6] but this may be delayed or prevented by using it as an adjunct to other antiepileptics. Acetazolamide has been successfully used in management of seizures in children from 1 year of age.[5]

1. Resor SR, Resor LD. Chronic acetazolamide monotherapy in the treatment of juvenile myoclonic epilepsy. *Neurology* 1990; **40:** 1677–81.
2. Reiss WG, Oles KS. Acetazolamide in the treatment of seizures. *Ann Pharmacother* 1996; **30:** 514–19.
3. Hoddevik GH. Acetazolamid—verdt en renessanse i epilepsibehandlingen? *Tidsskr Nor Laegeforen* 2000; **120:** 1042–5.
4. Lim LL, *et al*. Acetazolamide in women with catamenial epilepsy. *Epilepsia* 2001; **42:** 746–9.
5. Katayama F, *et al*. Long-term effectiveness and side effects of acetazolamide as an adjunct to other anticonvulsants in the treatment of refractory epilepsies. *Brain Dev* 2002; **24:** 150–4.
6. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacol Rev* 1990; **42:** 223–86.

Glaucoma. Acetazolamide may be given orally or parenterally in the acute management of angle-closure glaucoma (p.1873) and to minimise rises in intra-ocular pressure associated with ocular surgery.[1,2] It may also be given orally in the long-term management of primary and secondary open-angle glaucoma but is usually used as a second-line drug and added to topical beta blockers. However, up to 50% of patients are unable to tolerate oral therapy because of adverse effects[3] although topical carbonic anhydrase inhibitors such as dorzolamide may be better tolerated. Attempts have been made to reduce the adverse effects of acetazolamide by modifying the dosage schedule. A single-dose study[4] showed that doses of acetazolamide greater than 63 mg produced no greater reductions in intra-ocular pressure in patients with ocular hypertension. Another study[5] reported that acetazolamide 250-mg tablets twice daily controlled intra-ocular pressure adequately while producing fewer adverse effects than 250 mg four times daily and it was suggested that there was no advantage in using the modified-release capsule formulation (500 mg twice daily). A study in patients with open-angle glaucoma[6] found that most patients were adequately controlled by a single night-time dose of acetazolamide 500 mg either as tablets or modified-release capsules. The night-time dose also reduced the severity of adverse effects compared with the same dose given in the morning, and could aid compliance.

1. Ladas ID, *et al*. Prophylactic use of acetazolamide to prevent intraocular pressure elevation following Nd-YAG laser posterior capsulotomy. *Br J Ophthalmol* 1993; **77:** 136–8.
2. Edmunds B, Canning CR. The effect of prophylactic acetazolamide in patients undergoing extensive retinal detachment repair. *Eye* 1996; **10:** 328–30.
3. Hurvitz LM, *et al*. New developments in the drug treatment of glaucoma. *Drugs* 1991; **41:** 514–32.
4. Friedland BR, *et al*. Short-term dose response characteristics of acetazolamide in man. *Arch Ophthalmol* 1977; **95:** 1809–12.
5. Ledger-Scott M, Hurst J. Comparison of the bioavailability of two acetazolamide formulations. *Pharm J* 1985; **235:** 451.
6. Joyce PW, Mills KB. Comparison of the effect of acetazolamide tablets and sustets on diurnal intraocular pressure in patients with chronic simple glaucoma. *Br J Ophthalmol* 1990; **74:** 413–16.

High-altitude disorders. Acetazolamide is the most frequently used drug for the prophylaxis of high-altitude disorders (p.1168). It accelerates the process of acclimatisation, thus reducing the incidence of acute mountain sickness and associated symptoms such as headache, nausea, vomiting, and lethargy. The optimum dose is not clear. A systematic review[1] concluded that 750 mg daily effectively prevented acute mountain sickness, but that a dose of 500 mg daily was not effective. However, these conclusions have been criticised, and a subsequent controlled study[2] found that a dose of 125 mg twice daily reduced the inci-

dence of acute mountain sickness by about 50%. Acetazolamide may also have some benefit in relieving symptoms once they have developed although experience is limited. It does not prevent or protect against pulmonary or cerebral oedema.

1. Dumont L, *et al.* Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ* 2000; **321:** 267–72.
2. Basnyat B, *et al.* Efficacy of low-dose acetazolamide (125 mg BID) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. *High Alt Med Biol* 2003; **4:** 45–52.

Macular oedema. For mention of the use of acetazolamide to treat macular oedema associated with uveitis, see Uveitis, p.1515.

Ménière's disease. In Ménière's disease (p.564) high concentrations of carbonic anhydrase are found in the labyrinth, and acetazolamide, a carbonic anhydrase inhibitor, has been tried for both diagnosis and treatment.[1] A dose of 500 mg by intravenous injection has been suggested for diagnosis of fluctuating Ménière's disease.[1] Oral treatment with the drug, however, has not been particularly effective and has been associated with a high incidence of adverse effects.[2]

1. Brookes GB. Ménière's disease: a practical approach to management. *Drugs* 1983; **25:** 77–89.
2. Brookes GB, Booth JB. Oral acetazolamide in Ménière's disease. *J Laryngol Otol* 1984; **98:** 1087–95.

Neuromuscular disorders. Acetazolamide may be of benefit in some neuromuscular disorders, including hypokalaemic periodic paralysis (p.1670). Doses of 375 to 500 mg daily were effective in 2 patients with severe paralysis and were well tolerated.[1] Preliminary observations in 5 other patients showed a striking improvement in 3. In a further 12 patients,[2] doses of 125 mg were given three times daily to children and 250 mg two to six times daily to adults. There was dramatic improvement in 10 of the 12 and this lasted for up to 43 months. Chronic weakness between attacks in 10 patients was improved in 8.

Acetazolamide may reduce the frequency of attacks in patients with hyperkalaemic periodic paralysis (p.1669). It has also been used in episodic ataxia.[3]

1. Resnick JS, *et al.* Acetazolamide prophylaxis in hypokalemic periodic paralysis. *N Engl J Med* 1968; **278:** 582–6.
2. Griggs RC, *et al.* Acetazolamide treatment of hypokalemic periodic paralysis: prevention of attacks and improvement of persistent weakness. *Ann Intern Med* 1970; **73:** 39–48.
3. Melberg A, *et al.* Loss of control after a cup of coffee. *Lancet* 1997; **350:** 1220.

Raised intracranial pressure. Acetazolamide has been used to reduce raised intracranial pressure (p.1181). It has a role in the management of idiopathic intracranial hypertension. It has also been tried in the treatment of immunocompromised patients with chronically raised intracranial pressure due to cryptococcal meningitis,[1] although a controlled trial[2] was terminated early due to serious adverse events possibly due to additive toxicity with amphotericin. However, acetazolamide was used successfully for long-term treatment in 2 immunocompetent patients[3] with raised intracranial pressure following fungal meningitis.

The *BNFC* suggests an initial dose of 8 mg/kg of acetazolamide 3 times daily for the treatment of raised intracranial pressure in children aged 1 month to 12 years; the dose may be increased to a maximum of 100 mg/kg daily as necessary. Acetazolamide may be given orally or by slow intravenous injection.

1. Johnston SRD, *et al.* Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. *J Infect* 1992; **24:** 185–9.
2. Newton PN, *et al.* A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis* 2002; **35:** 769–72.
3. Patel S, *et al.* Acetazolamide therapy and intracranial pressure. *Clin Infect Dis* 2002; **36:** 538.

Preparations

BP 2008: Acetazolamide Tablets;
USP 31: Acetazolamide for Injection; Acetazolamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Diamox; ***Austral.:*** Diamox; ***Austria:*** Diamox; ***Belg.:*** Diamox; ***Braz.:*** Diamox; Zolamox; ***Canad.:*** Diamox; ***Cz.:*** Diluran; ***Denm.:*** Diamox†; ***Fin.:*** Diamox; Odemin; ***Fr.:*** Defiltran; Diamox; ***Ger.:*** Diamox; Diuramid; Glaupax; ***Gr.:*** Diamox; ***Hong Kong:*** Diamox; ***Hung.:*** Huma-Zolamide; ***India:*** Diamox; ***Indon.:*** Diamox; ***Irl.:*** Diamox; ***Israel:*** Diamox†; Uramox; ***Ital.:*** Diamox; ***Mex.:*** Aceta-Diazol; Akezol; Diamox†; ***Neth.:*** Diamox; Glaupax†; ***Norw.:*** Diamox; ***NZ:*** Diamox; ***Philipp.:*** Cetamid; Diamox; ***Pol.:*** Diuramid; ***Port.:*** Carbinib; ***Rus.:*** Diacarb (Диакарб); ***S.Afr.:*** Azomid; Diamox; ***Spain:*** Edemox; ***Swed.:*** Diamox†; ***Switz.:*** Diamox; Glaupax; ***Thai.:*** Diamox; ***Turk.:*** Diazomid; ***UK:*** Diamox; ***USA:*** Dazamide†; Diamox; ***Venez.:*** Diamox†.

Acetylcholine Chloride *(BAN, rINN)*

Aceticholino chloridas; Acetilkolin-klorid; Acetylcholin chlorid; Acétylcholine, chlorure d'; Acetylcholini chloridum; Acetylkolinklorid; Acetylocholiny chlorek; Asetilkolin Klorür; Asetyylikoliinikloridi; Cloruro de acetilcolina. (2-Acetoxyethyl)trimethylammonium chloride.

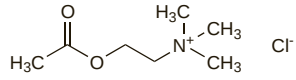
Ацетилхолина Хлорид

$C_7H_{16}ClNO_2$ = 181.7.

CAS — 51-84-3 (acetylcholine); 60-31-1 (acetylcholine chloride).

ATC — S01EB09.

ATC Vet — QS01EB09.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Jpn includes Acetylcholine Chloride for Injection.
Ph. Eur. 6.2 (Acetylcholine Chloride). A very hygroscopic, white or almost white crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Protect from light.
USP 31 (Acetylcholine Chloride). White or off-white crystals or crystalline powder. Very soluble in water; freely soluble in alcohol; insoluble in ether. It is decomposed by hot water and by alkalis. Store in airtight containers.

Adverse Effects

Because it is rapidly hydrolysed in the body by cholinesterases the toxicity of acetylcholine is normally relatively low.

Systemic adverse effects of the choline esters include nausea and vomiting, abdominal pain, flushing, sweating, salivation, lachrymation, rhinorrhoea, eructation, diarrhoea, urinary frequency, headache, bradycardia, peripheral vasodilatation leading to hypotension, and bronchoconstriction.

Ocular adverse effects after local application of choline esters to the eye include corneal oedema, clouding, and decompensation, persistent bullous keratopathy, retinal detachment, and postoperative iritis.

Treatment of Adverse Effects

Atropine sulfate may be given intravenously, intramuscularly, or subcutaneously to control the muscarinic and most nicotinic effects of the choline esters. Supportive treatment may be required.

Precautions

Choline esters are generally contra-indicated for *systemic use* in intestinal or urinary obstruction or where increased muscular activity of the urinary or gastrointestinal tract is liable to be harmful. They are also contra-indicated in asthma and obstructive airways disease, in cardiovascular disorders including bradycardia or heart block and recent myocardial infarction, and in hypotension, vagotonia, epilepsy, parkinsonism, hyperthyroidism, peptic ulceration, and pregnancy. Choline esters should not be given by the intravenous or intramuscular routes as very severe muscarinic adverse effects are liable to occur, calling for emergency treatment with atropine.

Although acetylcholine is normally rapidly hydrolysed in the body, systemic effects have followed *topical application* of choline esters to the eye, albeit rarely, and caution is advisable in the above conditions.

Interactions

As for Neostigmine, p.632. Acetylcholine is hydrolysed in the body by cholinesterase and its effects are markedly prolonged and enhanced if given after anticholinesterases.

Beta blockers. Severe bronchospasm with subsequent pulmonary oedema was reported[1] after intra-ocular injection of acetylcholine chloride in a patient also receiving *metoprolol* by mouth.

1. Rasch D, *et al.* Bronchospasm following intraocular injection of acetylcholine in a patient taking metoprolol. *Anesthesiology* 1983; **59:** 583–5.

NSAIDs. According to licensed product information for acetylcholine chloride ophthalmic preparations, there have been reports that acetylcholine and carbachol were ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Uses and Administration

Acetylcholine is an endogenous chemical transmitter with a very wide range of actions in the body (see below). It is used as a miotic to reduce postoperative rises in intra-ocular pressure associated with cataract surgery, penetrating keratoplasty, iridectomy, and other anterior segment surgery (see p.1873) but is ineffective when applied topically as it is hydrolysed more rapidly than it can penetrate the cornea. Doses of 0.5 to 2 mL of a freshly prepared 1% solution of acetylcholine chloride are therefore instilled directly into the anterior chamber of the eye (intracameral instillation). Miosis occurs within seconds and lasts for about 20 minutes. A second application may be made if prolonged miosis is required.

Action. Acetylcholine is a powerful quaternary ammonium parasympathomimetic but its action is transient as it is rapidly destroyed by cholinesterase. It is released from postganglionic parasympathetic nerves and also from some postganglionic sympathetic nerves to produce peripheral actions which correspond to those of muscarine. It is accordingly a vasodilator and cardiac depressant, a stimulant of the vagus and the parasympathetic nervous system, and it has a tonic action on smooth muscle. It also increases lachrymal, salivary, and other secretions. All the muscarinic actions of acetylcholine are abolished by atropine.

Acetylcholine also has actions that correspond to those of nicotine and is accordingly a stimulant of skeletal muscle, the autonomic ganglia, and the adrenal medulla. The nicotinic actions of acetylcholine on skeletal muscle are blocked by competitive neuromuscular blockers; they are also inhibited by massive doses or discharge of acetylcholine itself, which has clinical application in relation to the mode of action of suxamethonium (p.1912).

Drugs that mimic or enhance the actions of acetylcholine in the body are known as **parasympathomimetics** and may be classified into 2 distinct pharmacological groups:

- **cholinergic agonists**, such as bethanechol, carbachol, methacholine, and pilocarpine which act directly on effector cells to mimic the effects of acetylcholine. They are sometimes referred to as cholinomimetics or true parasympathomimetics; some such as bethanechol, carbachol, and methacholine are choline esters
- **anticholinesterases** (cholinesterase inhibitors) which inhibit the enzymic hydrolysis of acetylcholine by acetylcholinesterase and other cholinesterases, thereby prolonging and enhancing its actions in the body. They may be classified by the length of time taken to restore active enzyme following binding of enzyme to drug. The 'reversible' anticholinesterases such as ambenonium, neostigmine, physostigmine, and pyridostigmine generally produce enzyme inhibition for a few hours, whereas 'irreversible' anticholinesterases such as dyflos and ecothiopate produce extremely prolonged inhibition, and return of cholinesterase activity depends on synthesis of new enzyme. Centrally acting reversible anticholinesterases include donepezil, galantamine, rivastigmine, and tacrine

Drugs such as fampridine and guanidine, which enhance the release of acetylcholine from nerve terminals, also have similar effects.

Diagnosis and testing. ***AUTONOMIC FAILURE.*** Acetylcholine has been used in a sweat-spot test for autonomic neuropathy in diabetic patients.[1] An area on the dorsum of the foot is painted with iodine and starch, followed by intradermal injection of acetylcholine into the centre of the area. Sweat produced in response to acetylcholine reacts with the iodine and starch to produce fine black dots corresponding to the pores of the sweat glands; a normal response is indicated by a uniform distribution of dark spots whereas in diabetic autonomic neuropathy this pattern is lost to a varying degree. A similar test has been carried out[2] to assess sympathetic nerve function and therefore predict the success of lumbar sympathectomy in patients with critical limb ischaemia.

1. Ryder REJ, *et al.* Acetylcholine sweatspot test for autonomic denervation. *Lancet* 1988; **i:** 1303–5.
2. Altomare DF. Acetylcholine sweat test: an effective way to select patients for lumbar sympathectomy. *Lancet* 1994; **344:** 976–8.

Preparations

USP 31: Acetylcholine Chloride for Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Miochol; ***Belg.:*** Miochole; ***Canad.:*** Miochol-E; Miochol†; ***Chile:*** Miochol-E†; ***Fin.:*** Miochol-E; ***Fr.:*** Miochole; ***Ger.:*** Miochol-E; ***Gr.:*** Miochol-E; ***Hong Kong:*** Miochol-E; ***Indon.:*** Miochol-E; ***Irl.:*** Miochol; ***Israel:*** Miochol; Miochol-E; ***Ital.:*** Miochol-E; Miovisin; ***Mex.:*** Iloc; ***Neth.:*** Miochol; ***NZ:*** Miochol; ***Port.:*** Miochol; ***S.Afr.:*** Covochol; Miochol; ***Singapore:*** Miochol-E†; ***Swed.:*** Miochol-E; ***Switz.:*** Miochol; ***Thai.:*** Miochol†; ***Turk.:*** Miochol-E; ***UK:*** Miochol; ***USA:*** Miochol.

Apraclonidine Hydrochloride

(BANM, USAN, rINNM)

AL-02145 (apraclonidine); *p*-Aminoclonidine Hydrochloride; Aplonidine Hydrochloride; Apraclonidine, chlorhydrate d'; Apraclonidini hydrochloridum; Hidrocloruro de apraclonidina; NC-14. 2-[(4-Amino-2,6-dichlorophenyl)imino]imidazolidine hydrochloride; 2,6-Dichloro-*N*^{1}-imidazolidin-2-ylidene-*p*-phenylenediamine hydrochloride.

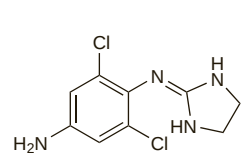
Апраклонидина Гидрохлорид

$C_9H_{10}Cl_2N_4,HCl$ = 281.6.

CAS — 66711-21-5 (apraclonidine); 73218-79-8 (apraclonidine hydrochloride).

ATC — S01EA03.

ATC Vet — QS01EA03.



(apraclonidine)

NOTE. APR is a code approved by the BP 2008 for use on single unit doses of eye drops containing apraclonidine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.