For *topical anaesthesia*, a 4% gel is used as a *percutaneous local anaesthetic* before *venepuncture or venous cannulation*. The gel is applied to the centre of the area to be anaesthetised and covered with an occlusive dressing. Gel and dressing are removed after 30 minutes for venepuncture and after 45 minutes for venous cannulation. A single application generally provides anaesthesia for 4 to 6 hours. This method is not suitable for premature infants or those less than 1 month of age. A transdermal patch containing tetracaine 70 mg with lidocaine 70 mg is available for surface anaesthesia of intact skin in connection with *needle puncture* and in cases of *superficial surgical procedures*. A cream or an ointment has been used for painful conditions of the *anus or rectum*.

Tetracaine hydrochloride has also been used in the *mouth* in sprays and lozenges.

Tetracaine hydrochloride has also been used for *spinal block* usually as a 0.5% solution.

Action. For a comparison of the vasoactivity of tetracaine with some other local anaesthetics, see p.1852.

Spinal block. A study[1] in 40 patients indicated that for patients undergoing caesarean section with spinal anaesthesia (see Central Nerve Block, p.1853) doses of 12 or 14 mg of tetracaine provided better intraoperative analgesia than doses of 8 or 10 mg without leading to excessive spread of the block.

1. Hirabayashi Y, *et al.* Visceral pain during Caesarean section: effect of varying dose of spinal amethocaine. *Br J Anaesth* 1995; **75:** 266–8.

Surface anaesthesia. A topical gel formulation of tetracaine 4% appears to provide more rapid and prolonged surface anaesthesia (see p.1853) than a eutectic mixture of lidocaine and prilocaine.[1,2] In a double-blind placebo-controlled study[3] the tetracaine gel formulation was significantly better than the eutectic mixture in reducing pain caused by laser treatment of portwine stains. Similar findings were also seen in a comparative study[4] and a systematic review[5] in children requiring venous cannulation, although others have questioned the efficacy of tetracaine gel in peripheral insertion of a central catheter.[6] The same formulation appears to be effective when incorporated into a transdermal patch.[7] Patches containing a mixture of lidocaine and tetracaine have also been tried[8,9] and are licensed in some countries for surface anaesthesia of intact skin in connection with needle puncture and in cases of superficial surgical procedures.

There have been reports of seizures and death in children after the use of a mixture of tetracaine, adrenaline, and cocaine on mucosal surfaces;[10] application of preparations of tetracaine to highly vascular surfaces is contra-indicated. A gel containing a mixture of lidocaine, adrenaline, and tetracaine has been found to be an effective alternative to the cocaine-containing preparation.[11]

Tetracaine has also been incorporated into a mucosa-adhesive polymer film to relieve the pain of oral lesions resulting from radiation and antineoplastic therapy.[12] Liposome-encapsulated tetracaine has also been shown to provide adequate surface anaesthesia.[13]

1. McCafferty DF, *et al.* In vivo assessment of percutaneous local anaesthetic preparations. *Br J Anaesth* 1989; **62:** 17–21.
2. Rømsing J, *et al.* Tetracaine gel vs EMLA cream for percutaneous anaesthesia in children. *Br J Anaesth* 1999; **82:** 637–8.
3. McCafferty DF, *et al.* Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains. *Br J Anaesth* 1997; **78:** 286–9.
4. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. *Arch Dis Child* 2000; **82:** 309–10.
5. Lander JA, *et al.* EMLA and amethocaine for reduction of children's pain associated with needle insertion. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/04/08).
6. Lemyre B, *et al.* How effective is tetracaine 4% gel, before a peripherally inserted central catheter, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial. *BMC Med* 2006; **4:** 11. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-4-11.pdf (accessed 21/06/06)
7. McCafferty DF, Woolfson AD. New patch delivery system for percutaneous local anaesthesia. *Br J Anaesth* 1993; **71:** 370–4.
8. Berman B, *et al.* Self-warming lidocaine/tetracaine patch effectively and safely induces local anesthesia during minor dermatologic procedures. *Dermatol Surg* 2005; **31:** 135–8.
9. Schecter AK, *et al.* Randomized, double-blind, placebo-controlled study evaluating the lidocaine/tetracaine patch for induction of local anesthesia prior to minor dermatologic procedures in geriatric patients. *Dermatol Surg* 2005; **31:** 287–91.
10. Wong S, Hart LL. Tetracaine/adrenaline/cocaine for local anesthesia. *DICP Ann Pharmacother* 1990; **24:** 1181–3.
11. Ernst AA, *et al.* Lidocaine adrenaline tetracaine gel versus tetracaine adrenaline cocaine gel for topical anesthesia in linear scalp and facial lacerations in children aged 5 to 17 years. *Pediatrics* 1995; **95:** 255–8.
12. Yotsuyanagi T, *et al.* Mucosa-adhesive film containing local analgesic. *Lancet* 1985; **ii:** 613.
13. Fisher R, *et al.* Topical anaesthesia of intact skin: liposome-encapsulated tetracaine vs EMLA. *Br J Anaesth* 1998; **81:** 972–3.

Preparations

BP 2008: Tetracaine Eye Drops;
USP 31: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Tetracaine and Menthol Ointment; Tetracaine Hydrochloride Cream; Tetracaine Hydrochloride for Injection; Tetracaine Hydrochloride in Dextrose Injection; Tetracaine Hydrochloride Injection; Tetracaine Hydrochloride Ophthalmic Solution; Tetracaine Hydrochloride Topical Solution; Tetracaine Ointment; Tetracaine Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Tray-Te; ***Braz.:*** Anestesico; ***Canad.:*** Ametop; Cepacol Viractin†; Pontocaine; Viractin; ***Fr.:*** Solutricine Maux de Gorge; ***Ger.:*** Ophtocain N; ***Hong Kong:*** Ametop; ***Irl.:*** Ametop†; ***Israel:*** Pontocaine†; ***Mex.:*** Ponti; ***NZ:*** Ametop†; ***S.Afr.:*** Covostet; ***Spain:*** Anestesia Topi Braun C/A; Anestesia Topi Braun S/A; Anestesico; Hemonet; Lubricante Urol; ***Swed.:*** Tetrakain; ***UK:*** Ametop; Anethaine; ***USA:*** Cepacol Viractin Cold Sore Treatment; Pontocaine.

Multi-ingredient: ***Arg.:*** Bagociletas con Anestesia; Clevosan; Drill; ***Austria:*** Dynexan; Herviros; Neocones; ***Braz.:*** Anesdente do Bebe†; Anestesiol†; Hexomedine; Oto Betnovate; Oto-Biotic†; Um Instante†; ***Canad.:*** Endospray†; ***Cz.:*** Drill; ***Fr.:*** Aphtoral; Broncorinol maux de gorge†; Cantalene; Codetricine vitamine C†; Drill; Eludril; Hexomedine†; Oromedine; Solutricine Maux de Gorge; ***Ger.:*** Acoin; Gingicain D; Herviros†; ***Hung.:*** Drill; ***Israel:*** Anaesthetic Ear Drops; Otidin; ***Ital.:*** Corizzina†; Donalg; Odongi; Recto-Reparil; Ruscoroid; ***NZ:*** Topicaine; ***Pol.:*** Ruskorex; ***Port.:*** Anucet; Colircusi Anestesico; Drill; Hemofissural; Lubrificante Anestesico; Rapydan; Xilonibsa†; ***Rus.:*** Drill (Дрилл); ***S.Afr.:*** Dynexan; ***Spain:*** Anestesi Doble; Blastoestimulina; Carbocaina†; Dentiknsos; Neocones; Otogen Calmante; Resorborina; Topicaina†; Vinciseptil Otico; ***Switz.:*** Angidine; Eludril; Tyrothricine + Gramicidine; ***Turk.:*** Hemoralgine; Otimisin; ***UK:*** Eludril; Rapydan; ***USA:*** Cetacaine; Pliaglis; Stypto-Caine; Synera.

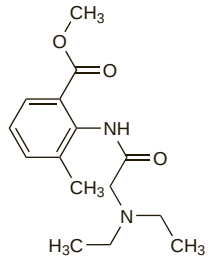
Tolycaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tolicaína; Tolycaïne, Chlorhydrate de; Tolycaini Hydrochloridum. Methyl 2-(2-diethylaminoacetamido)-*m*-toluate hydrochloride.

Толикаина Гидрохлорид

$C_{15}H_{22}N_2O_3$,HCl = 314.8.

CAS — 3686-58-6 (tolycaine); 7210-92-6 (tolycaine hydrochloride).



(tolycaine)

Profile

Tolycaine hydrochloride is an amide local anaesthetic (p.1850) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: ***Ger.:*** Tardocillin.

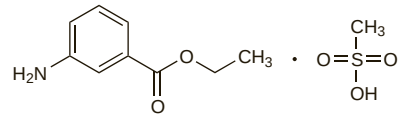
Tricaine Mesilate

Metacaine Mesylate; Tricaína, mesilato de; Tricaine Mesylate; TS-222. Ethyl 3-aminobenzoate methanesulphonate.

$C_{10}H_{15}NO_5S$ = 261.3.

CAS — 886-86-2.

ATC Vet — QN01AX93.



Profile

Tricaine mesilate is a derivative of an isomer of benzocaine (see p.1854) and although it has been used as a local anaesthetic in human medicine it is now mainly used as an anaesthetic and tranquilliser for fish and other cold-blooded animals.

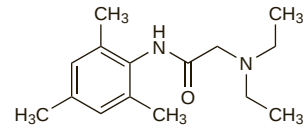
Trimecaine Hydrochloride *(rINNM)*

Hidrocloruro de trimecaína; Trimécaïne, Chlorhydrate de; Trimecaini Hydrochloridum; Trimecainium Chloratum; Trimekain-hydrochlorid. 2-Diethylamino-2′,4′,6′-trimethylacetanilide hydrochloride.

Тримекаина Гидрохлорид

$C_{15}H_{24}N_2O$,HCl = 284.8.

CAS — 616-68-2 (trimecaine); 1027-14-1 (trimecaine hydrochloride).



(trimecaine)

Profile

Trimecaine hydrochloride is an amide local anaesthetic (p.1850) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Mesocain.

Multi-ingredient: ***Cz.:*** Mesocain; Septonex Plus; ***Rus.:*** Levosin (Левосин); Simetrid (Симетрид).

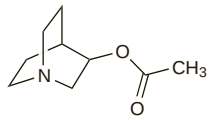
Used as an adjunct in: ***Austria:*** Ketazon†.

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†.

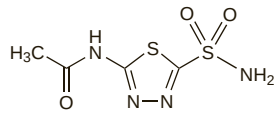
Multi-ingredient: ***Ital.:*** Glautimol.

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