4. Fontana GA, Pistolesi M. Chronic cough and gastro-oesophageal reflux. *Thorax* 2003; **58:** 1092–5.
5. Dicpinigaitis PV. Cough in asthma and eosinophilic bronchitis. *Thorax* 2004; **59:** 71–2.
6. Belvisi MG, Geppetti P. Cough 7: current and future drugs for the treatment of cough. *Thorax* 2004; **59:** 438–40.
7. Morice AH, *et al.* The diagnosis and management of chronic cough. *Eur Respir J* 2004; **24:** 481–92.
8. Irwin RS, *et al.* American College of Chest Physicians. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129** (suppl): 1S–23S. Also available at: http://www.chestjournal.org/cgi/reprint/129/1_suppl/1S.pdf (accessed 11/05/07)
9. Bolser DC. American College of Chest Physicians. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129** (suppl): 238S–249S. Also available at: http://www.chestjournal.org/cgi/reprint/129/1_suppl/238S.pdf (accessed 11/05/07)
10. Morice AH, *et al.* British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. *Thorax* 2006; **61** (suppl): i1–i24. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/coughguidelinesaugust06.pdf (accessed 15/07/08)
11. Pavord ID, Chung KF. Management of chronic cough. *Lancet* 2008; **371:** 1375–84.
12. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 16/04/08).
13. Shields MD, *et al.* British Thoracic Society Cough Guideline Group. BTS guidelines: Recommendations for the assessment and management of cough in children. *Thorax* 2008; **63** (suppl III): iii1–iii15. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/cough_in_children.pdf (accessed 15/07/08)
14. FDA. FDA releases recommendations regarding use of over-the-counter cough and cold products (issued 17th January, 2008). Available at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01778.html (accessed 15/04/08)
15. MHRA/CHM. Updated advice—over-the-counter cough and cold medicines for children. *Drug Safety Update* 2008; **1** (9): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 15/04/08)

Nasal congestion

Nasal congestion is frequently a symptom of conditions such as rhinitis (p.565), treatment of which can include the use of antihistamines, sympathomimetics, corticosteroids, antimuscarinics, and cromoglicate or nedocromil.

Sympathomimetics are also widely used as nasal decongestants to provide symptomatic relief of the common cold (p.850). They are used for the vasoconstriction produced by their alpha-adrenergic effects; redistribution of local blood flow reduces oedema of the nasal mucosa, thus improving ventilation, drainage, and nasal stuffiness. Sympathomimetics such as ephedrine, phenylephrine, naphazoline, oxymetazoline, and xylometazoline can be used topically as nasal drops or sprays. Those such as pseudoephedrine are given orally. Over-the-counter cough and cold preparations containing sympathomimetic decongestants should be used with caution in children and generally avoided in those under 2 years of age (see above). However, the *BNFC* suggests that, in certain circumstances, specialists may prescribe ephedrine or xylometazoline nasal drops for children under 2 years in the short-term treatment of severe nasal congestion that has not responded to sodium chloride nasal drops or inhalation of warm moist air (see below).

Topical use, particularly if prolonged, may lead to rebound congestion as vasodilatation becomes prominent and the effects of vasoconstriction subside. Use is therefore restricted to periods of not more than 7 consecutive days. Oral use is not associated with such rebound congestion, but is more likely to be associated with systemic adverse effects and a higher risk of drug interactions. A systematic review found no difference in efficacy between oral and topical decongestants from the limited evidence available.[1]

The benefits of *antihistamines* in nasal congestion other than that associated with allergic rhinitis are doubtful, particularly by topical application.

Inhalations of warm moist air are also useful in the treatment of nasal congestion associated with the common cold. As in the case of cough (see above) the addition of substances such as menthol, benzoin, or volatile oils may encourage the use of such inhalations. Sodium chloride nasal drops may also be effective, particularly in infants and young children.

1. Taverner D, Latte J. Nasal decongestants for the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/07/08).

Acetylcysteine *(BAN, USAN, rINN)*

5052; Acetilcisteína; Acetilcisteinas; Acetilcisztein; Acetylcystein; Acétylcystéine; Acetylcysteinum; Asetilsistein; Asetyylikysteiini; NSC-111180. *N*-Acetyl-L-cysteine.

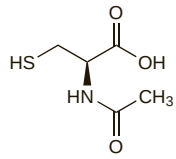
Ацетилцистеин

$C_5H_9NO_3S$ = 163.2.

CAS — 616-91-1.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.



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

Ph. Eur. 6.2 (Acetylcysteine). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 2.8. Protect from light.

USP 31 (Acetylcysteine). A white crystalline powder having a slight acetic odour. Soluble 1 in 5 of water and 1 in 4 of alcohol; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 2.0 and 2.8. Store in airtight containers.

Incompatibility. Acetylcysteine is incompatible with some metals, including iron and copper, with rubber, and with oxygen and oxidising substances. Some antimicrobials including amphotericin B, ampicillin sodium, erythromycin lactobionate, and some tetracyclines are either physically incompatible with, or may be inactivated on mixture with, acetylcysteine.

Stability. A change in colour of solutions of acetylcysteine to light purple does not indicate significant impairment of safety or efficacy.

Acetylcysteine Sodium *(BANM, rINNM)*

Acetilcisteína sódica; Acétylcystéine Sodique; Natrii Acetylcysteinum.

Натрий Ацетилцистеин

$C_5H_8NNaO_3S$ = 185.2.

CAS — 19542-74-6.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.

Adverse Effects

Hypersensitivity reactions have been reported in patients receiving acetylcysteine, including bronchospasm, angioedema, rashes and pruritus; hypotension, or occasionally hypertension, may occur. Other adverse effects reported with acetylcysteine include flushing, nausea and vomiting, fever, syncope, sweating, arthralgia, blurred vision, disturbances of liver function, acidosis, convulsions, and cardiac or respiratory arrest. Haemoptysis, rhinorrhoea, and stomatitis have been associated with inhalation of acetylcysteine.

Hypersensitivity. The most common symptoms of patients experiencing **anaphylactoid** reactions after the intravenous use of acetylcysteine in the treatment of paracetamol poisoning are rash and pruritus; other features have included flushing, nausea or vomiting, angioedema, tachycardia, bronchospasm, hypotension, and hypertension;[1-3] ECG abnormalities associated with an anaphylactoid reaction have also been reported in a patient.[4] Anaphylactoid reactions to intravenous acetylcysteine appear to be dose-related.[5] One group estimated that when acetylcysteine was given correctly the **frequency** of the anaphylactoid response was between 0.3 and 3%, whereas 11 of 15 patients who had received an overdose had an anaphylactoid reaction.[6] Intradermal testing and study of plasma-acetylcysteine concentrations in patients who developed reactions to acetylcysteine suggests a 'pseudo-allergic' rather than an immunological reaction,[7,8] although symptoms consistent with a serum sickness-like illness developed after exposure to acetylcysteine in one patient.[9] It has been suggested that generalised reactions to acetylcysteine can be **treated** with intravenous injection of an antihistamine;[5,10] infusion of acetylcysteine should be temporarily stopped but can usually be restarted at a slower rate without further reaction.[3]

Symptoms after **overdosage** with acetylcysteine have been more severe. Hypotension appears to be especially prominent;[6] additional symptoms have included respiratory depression, haemolysis, disseminated intravascular coagulation, and renal failure, but some of these may have been due to paracetamol poisoning.[1] Death occurred in 3 patients who received an overdose of acetylcysteine while being treated for paracetamol poisoning,[1,11] but in 2 of them the role of acetylcysteine in this outcome was unclear.

1. Mant TGK, *et al.* Adverse reactions to acetylcysteine and effects of overdose. *BMJ* 1984; **289:** 217–19.
2. Dawson AH, *et al.* Adverse reactions to N-acetylcysteine during treatment for paracetamol poisoning. *Med J Aust* 1989; **150:** 329–31.
3. Pizon AF, LoVecchio F. Adverse reaction from use of intravenous N-acetylcysteine. *J Emerg Med* 2006; **31:** 434–5.
4. Bonfiglio MF, *et al.* Anaphylactoid reaction to intravenous acetylcysteine associated with electrocardiographic abnormalities. *Ann Pharmacother* 1992; **26:** 22–5.
5. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 1998; **31:** 710–15.
6. Sunman W, *et al.* Anaphylactoid response to intravenous acetylcysteine. *Lancet* 1992; **339:** 1231–2.
7. Bateman DN, *et al.* Adverse reactions to N-acetylcysteine. *Hum Toxicol* 1984; **3:** 393–8.
8. Donovan JW, *et al.* Adverse reactions of N-acetylcysteine and their relation to plasma levels. *Vet Hum Toxicol* 1987; **29:** 470.
9. Mohammed S, *et al.* Serum sickness-like illness associated with N-acetylcysteine therapy. *Ann Pharmacother* 1994; **28:** 285.
10. Bateman DN. Adverse reactions to antidotes. *Adverse Drug React Bull* 1988; (Dec.): 496–9.
11. Anonymous. Death after N-acetylcysteine. *Lancet* 1984; **i:** 1421.

Precautions

Acetylcysteine should be used with caution in asthmatic patients. It should also be used with caution in patients with a history of peptic ulcer disease, both because drug-induced nausea and vomiting may increase the risk of gastrointestinal haemorrhage in patients predisposed to the condition, and because of a theoretical risk that mucolytics may disrupt the gastric mucosal barrier.

Asthma. Bronchospasm precipitated in 2 asthmatic patients[1] and severe asthma and respiratory arrest in another[2] have been reported after intravenous treatment with acetylcysteine. There is also a report of a patient with brittle asthma who had a similar reaction and subsequently died after receiving intravenous treatment with acetylcysteine.[3] The increased risk does not justify delaying or witholding acetylcysteine in asthmatic patients with paracetamol poisoning, but consideration might be given to initial intravenous infusion over 30 to 60 minutes rather than the conventional 15 minutes.[4] However, a large multicentre study found no benefit from the more prolonged infusion—see Paracetamol under Poisoning and Toxicity, below.

1. Ho SW-C, Beilin LJ. Asthma associated with N-acetylcysteine infusion and paracetamol poisoning: report of two cases. *BMJ* 1983; **287:** 876–7.
2. Reynard K, *et al.* Respiratory arrest after N-acetylcysteine for paracetamol overdose. *Lancet* 1992; **340:** 675.
3. Appelboam AV, *et al.* Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. *Emerg Med J* 2002; **19:** 594–5.
4. Schmidt LE, Dalhoff K. Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Br J Clin Pharmacol* 2001; **51:** 87–91.

Hepatic impairment. The total clearance of acetylcysteine in patients with cirrhosis was found to be markedly impaired, and the elimination half-life almost twice that of healthy controls.[1] Since some of the more serious adverse effects of acetylcysteine occur when plasma concentrations are high, the authors considered that increased vigilance for untoward anaphylactoid reactions and other adverse effects was necessary in patients with cirrhosis receiving acetylcysteine, and further studies to determine the optimum dosage regimen in such patients were required.

1. Jones AL, *et al.* Pharmacokinetics of N-acetylcysteine are altered in patients with chronic liver disease. *Aliment Pharmacol Ther* 1997; **11:** 787–91.

Pharmacokinetics

◊ Acetylcysteine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 0.5 to 1 hour after oral doses of 200 to 600 mg.[1] Some studies indicate dose-dependent pharmacokinetics with peak concentrations, the time taken to reach peak concentrations, and bioavailability increasing with increasing doses.[2] Acetylcysteine may be present in plasma as the parent compound or as various oxidised metabolites such as *N*-acetylcystine, *N*,*N*-diacetylcystine, and cysteine either free or bound to plasma proteins by labile disulfide bonds or as a fraction incorporated into protein peptide chains.[3] In a study about 50% was in a covalently protein-bound form 4 hours after a dose.[4] Oral bioavailability is low and mean values have ranged from 4 to 10% depending on whether total acetylcysteine or just the reduced forms are measured.[4,5] It has been suggested that acetylcysteine's low oral bioavailability may be due to metabolism in the gut wall and first-pass metabolism in the liver.[4,5] Renal clearance may account for about 30% of total body clearance.[5] On intravenous dosage mean terminal half-lives have been calculated to be 1.95 and 5.58 hours for reduced and total acetylcysteine, respectively; the terminal half-life of total acetylcysteine was 6.25 hours after oral doses.[4]

For reference to altered pharmacokinetics in patients with hepatic impairment, see above.

1. Holdiness MR. Clinical pharmacokinetics of N-acetylcysteine. *Clin Pharmacokinet* 1991; **20:** 123–34.
2. Borgström L, Kågedal B. Dose dependent pharmacokinetics of N-acetylcysteine after oral dosing to man. *Biopharm Drug Dispos* 1990; **11:** 131–6.
3. De Caro L, *et al.* Pharmacokinetics and bioavailability of oral acetylcysteine in healthy volunteers. *Arzneimittelforschung* 1989; **39:** 383–6.
4. Olsson B, *et al.* Pharmacokinetics and bioavailability of reduced and oxidized N-acetylcysteine. *Eur J Clin Pharmacol* 1988; **34:** 77–82.
5. Borgström L, *et al.* Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol* 1986; **31:** 217–22.

Uses and Administration

Acetylcysteine is a mucolytic that reduces the viscosity of secretions probably by the splitting of disulfide bonds in mucoproteins. This action is greatest at a pH of 7 to 9 and the pH may have been adjusted in commercial preparations with sodium hydroxide. It is sometimes stated that acetylcysteine sodium is used, although the dose is expressed in terms of acetylcysteine.

Acetylcysteine is also able to promote the detoxification of an intermediate paracetamol metabolite, and has a key role in the management of paracetamol overdosage.

Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough. It can be given by nebulisation of 3 to 5 mL of a 20% solution or 6 to 10 mL of a 10% solution through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution or 2 to 20 mL of a 10% solution may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour. Mechanical suction of the liquefied secretions may be necessary, and nebulisers containing iron, copper, or rubber components should not be used.

Acetylcysteine as a mucolytic is also given orally, as lozenges, or as granules or effervescent tablets dissolved in water, in a usual dose of 600 mg daily as a single dose or in 3 divided doses.

In the treatment of **dry eye** (p.2140) associated with abnormal mucus production, acetylcysteine, usually as a 5% solution with hypromellose, is given topically 3 or 4 times daily. Higher concentrations have been used in some centres.

Acetylcysteine is given by intravenous infusion or by mouth in the treatment of **paracetamol poisoning**.

- If given intravenously: 150 mg/kg of acetylcysteine in 200 mL of glucose 5% is given initially over 15 minutes, followed by infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg in one litre of glucose 5% over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable.
- If given orally: an initial dose of 140 mg/kg as a 5% solution is followed by 70 mg/kg every 4 hours for an additional 17 doses.

Acetylcysteine is reported to be most effective when given within 8 hours of paracetamol overdosage, with the protective effect diminishing after this time. However, starting treatment with acetylcysteine later (up to and beyond 24 hours) may still be of benefit (see also below).

Acetylcysteine is under investigation for the treatment of idiopathic pulmonary fibrosis (see Diffuse Parenchymal Lung Disease, below).

For administration in children, see below.

◊ Reviews.

1. Atkinson MC. The use of N-acetylcysteine in intensive care. *Crit Care Resusc* 2002; **4:** 21–7.
2. Dekhuijzen PNR. Antioxidant properties of *N*-acetylcysteine: their relevance in relation to chronic obstructive pulmonary disease. *Eur Respir J* 2004; **23:** 629–36.
3. Guerin J-C, *et al.* Le stress oxydatif en pathologie broncho-pulmonaire : apport de la N-acétyl-cystéine (NAC). *Rev Pneumol Clin* 2005; **61:** 16–21.
4. Aitio M-L. N-acetylcysteine—passe-partout or much ado about nothing? *Br J Clin Pharmacol* 2006; **61:** 5–15.
5. Dekhuijzen PN. Acetylcysteine in de behandeling van ernstige COPD. *Ned Tijdschr Geneeskd* 2006; **150:** 1222–6.

Administration in children. Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough. Doses in children are similar to adults; 3 to 5 mL of a 20% solution, or 6 to 10 mL of a 10% solution, may be nebulised through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution, or 2 to 20 mL of a 10% solution, may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour.

Acetylcysteine has also been given orally in a variety of dosage forms. Licensed doses and age ranges vary somewhat from country to country and even from preparation to preparation. For example, in France, children may be given the following doses:

- 1 month to 2 years: 100 mg twice daily
- 2 to 7 years: 200 mg twice daily
- 7 years and over: 200 mg 3 times daily (adult dose)

In Germany and Switzerland, however, a more typical dose for children under 2 years of age is 50 mg two or three times daily.

Acetylcysteine has been used to treat meconium ileus in neonates and distal obstruction syndrome in children with **cystic fibrosis**, although the *BNFC* states that evidence of its efficacy is lacking. Such use is not licensed in the UK, but if it is to be used the *BNFC* suggests an oral dose of acetylcysteine 200 to 400 mg up to 3 times daily for meconium ileus in neonates. For the *treatment* of distal intestinal obstruction syndrome in children with cystic fibrosis, a single oral dose is recommended as follows:

- 1 month to 2 years: 400 mg to 3 g
- 2 to 7 years: 2 to 3 g
- 7 to 18 years: 4 to 6 g

For the *prevention* of distal intestinal obstruction syndrome, it is recommended to be given orally as follows:

- 1 month to 2 years: 100 to 200 mg 3 times daily
- 2 to 12 years: 200 mg 3 times daily
- 12 to 18 years: 200 to 400 mg 3 times daily

The injection may be used orally, diluted to a concentration of 50 mg/mL; orange or black currant juice or cola may be used as diluents to mask the bitter taste.

In the treatment of **dry eye** associated with impaired or abnormal mucus production, acetylcysteine 5% eye drops with hypromellose may be applied, as in adults, 3 or 4 times daily.

Acetylcysteine is given by intravenous infusion or by mouth in the treatment of **paracetamol poisoning**. Doses for children are similar to adults (see also above and on p.108), although the volume of intravenous fluid is modified. The *BNFC* suggests the following *intravenous* doses:

- neonates to 5 years (or body-weight under 20 kg): initially 150 mg/kg in 3 mL/kg glucose 5% given over 15 minutes, followed by 50 mg/kg in 7 mL/kg glucose 5% given over 4 hours, then 100 mg/kg in 14 mL/kg glucose 5% given over 16 hours
- 5 to 12 years (or body-weight over 20 kg): initially 150 mg/kg in 100 mL glucose 5% given over 15 minutes, followed by 50 mg/kg in 250 mL glucose 5% given over 4 hours, then 100 mg/kg in 500 mL glucose 5% given over 16 hours
- 12 to 18 years: adult dose

In the USA, the following *oral* dose has also been suggested for children: 140 mg/kg initially, followed by 70 mg/kg every 4 hours for an additional 17 doses.

Aspergillosis. Although it is not one of the standard therapies discussed on p.517, local instillation of acetylcysteine into the cavity containing the fungus ball has been used to treat aspergilloma.[1] There is some evidence *in vitro* that acetylcysteine has inhibitory properties against *Aspergillus* and *Fusarium* spp.[2]

1. Kauffman CA. Quandary about treatment of aspergillomas persists. *Lancet* 1996; **347:** 1640.
2. De Lucca AJ, *et al.* N-Acetylcysteine inhibits germination of conidia and growth of Aspergillus spp. and Fusarium spp. *Antimicrob Agents Chemother* 1996; **40:** 1274–6.

Burns. Children with inhalation injury (see Burns, p.1578) who were treated with aerosolised heparin 5000 units alternating with 3 mL of 20% acetylcysteine solution, inhaled every 2 hours for the first 7 days after injury, appeared to have significantly reduced mortality and reintubation rates compared with historical controls.[1]

1. Desai MH, *et al.* Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [sic] therapy. *J Burn Care Rehabil* 1998; **19:** 210–12. Correction. *ibid.* 1999; **20:** 49.

Cystic fibrosis. Mucolytics such as acetylcysteine are generally not considered[1] to be effective in treating the pulmonary manifestations of cystic fibrosis (p.166).

Meconium ileus equivalent (bowel obstruction due to abnormally viscid contents of the terminal ileum and right colon[2]) in patients with cystic fibrosis has largely disappeared with the use of pancreatic enzymes but may occur when insufficient doses are given;[3] mild cases may be treated with acetylcysteine.[3] Doses of 10 mL of a 20% solution of acetylcysteine have been given orally 4 times daily with 100 mL of a 10% solution of acetylcysteine given as an enema up to 4 times daily depending on the degree of the obstruction.[2]

For suggested children's doses in meconium ileus and distal obstruction syndrome, see Administration in Children, above.

1. Duijvestijn YC, Brand PL. Systematic review of N-acetylcysteine in cystic fibrosis. *Acta Paediatr* 1999; **88:** 38–41.
2. Hanly JG, Fitzgerald MX. Meconium ileus equivalent in older patients with cystic fibrosis. *BMJ* 1983; **286:** 1411–13.
3. David TJ. Cystic fibrosis. *Arch Dis Child* 1990; **65:** 152–7.

Diffuse parenchymal lung disease. Acetylcysteine is under investigation for the treatment of idiopathic pulmonary fibrosis (see Diffuse Parenchymal Lung Disease, p.1502). In a randomised controlled study, adjunctive treatment with acetylcysteine 600 mg three times daily by mouth slowed the loss of vital lung capacity compared with standard therapy with azathioprine and prednisone.[1]

1. Demedts M, *et al.* High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005; **353:** 2229–42.

HIV infection and AIDS. The cysteine-containing peptide glutathione is involved in intracellular defence mechanisms, and it has been shown that low glutathione concentrations are associated with poorer survival in HIV-infected patients.[1] Since acetylcysteine can replenish glutathione, it has been suggested[2,3] that it may have a role in the treatment of AIDS (p.856). *In-vitro* studies indicate that acetylcysteine can suppress HIV expression,[4,5] and there has been a suggestion from observational data that acetylcysteine supplements can improve survival in HIV-infected individuals.[1] However, an attempt to use acetylcysteine supplementation to reduce the frequency of adverse reactions to cotrimoxazole in HIV-infected patients was not successful.[6] Nonetheless, reviews of preliminary studies[7,8] have concluded that acetylcysteine may be a beneficial supplementary therapy in HIV-infected patients.

1. Herzenberg LA, *et al.* Glutathione deficiency is associated with impaired survival in HIV disease. *Proc Natl Acad Sci U S A* 1997; **94:** 1967–72.
2. Staal FJT, *et al.* Glutathione deficiency and human immunodeficiency virus infection. *Lancet* 1992; **339:** 909–12.
3. Roederer M, *et al.* N-acetylcysteine: potential for AIDS therapy. *Pharmacology* 1993; **46:** 121–9.
4. Roederer M, *et al.* Cytokine-stimulated human immunodeficiency virus replication is inhibited by N-acetyl-L-cysteine. *Proc Natl Acad Sci U S A* 1990; **87:** 4884–8.
5. Kalebic T, *et al.* Suppression of human immunodeficiency virus expression in chronically infected monocytic cells by glutathione, glutathione ester, and N-acetylcysteine. *Proc Natl Acad Sci U S A* 1991; **88:** 986–90.
6. Åkerlund B, *et al.* N-acetylcysteine treatment and the risk of toxic reactions to trimethoprim-sulphamethoxazole in primary Pneumocystis carinii prophylaxis in HIV-infected patients. *J Infect* 1997; **35:** 143–7.
7. Dröge W, Breitkreutz R. N-acetyl-cysteine in the therapy of HIV-positive patients. *Curr Opin Clin Nutr Metab Care* 1999; **2:** 493–8.
8. Patrick L. Nutrients and HIV: Part Three—N-acetylcysteine, alpha-lipoic acid, L-glutamine, and L-carnitine. *Altern Med Rev* 2000; **5:** 290–305.

Kidney disorders. Acetylcysteine has been reported to improve kidney function in patients with the hepatorenal syndrome and may offer a potential bridging therapy in such patients awaiting liver transplantation.[1] It has also been used in the prevention of contrast media-induced nephrotoxicity in patients with chronic renal impairment, but evidence of benefit is conflicting and its role remains to be established; see Effects on the Kidney under Adverse Effects of Amidotrizoic Acid (p.1476) for further details.

1. Holt S, *et al.* Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. *Lancet* 1999; **353:** 294–5.

Liver disorders. Although benefit has been reported from studies of acetylcysteine in acute liver failure,[1] and some have suggested that it may be useful in preventing tissue hypoxia in patients with acute liver failure receiving vasopressors,[2] studies have mainly been small and clinical outcomes are not well studied.[1] It does not appear to be of benefit in patients undergoing orthotopic liver transplantation.[3,4]

For reference to use in the hepatorenal syndrome, see Kidney Disorders, above. For use in paracetamol-induced liver damage see Overdosage, under Paracetamol, p.108.

1. Sklar GE, Subramaniam M. Acetylcysteine treatment for non-acetaminophen-induced acute liver failure. *Ann Pharmacother* 2004; **38:** 498–501.
2. Caraceni P, Van Thiel DH. Acute liver failure. *Lancet* 1995; **345:** 163–9.
3. Bromley PN, *et al.* Effects of intraoperative N-acetylcysteine in orthotopic liver transplantation. *Br J Anaesth* 1995; **75:** 352–4.
4. Steib A, *et al.* Does N-acetylcysteine improve hemodynamics and graft function in liver transplantation? *Liver Transpl Surg* 1998; **4:** 152–7.

Meconium ileus. For the use of acetylcysteine in infants with meconium ileus see Cystic Fibrosis, above.

Myocardial infarction. Some studies suggest that addition of intravenous acetylcysteine to thrombolytic therapy in patients with acute myocardial infarction (p.1175) may be of benefit.[1,2] The value of acetylcysteine as an adjunct in patients with or at risk of myocardial infarction has been reviewed.[3,4]

1. Arstall MA, *et al.* N-Acetylcysteine in combination with nitroglycerin and streptokinase for the treatment of evolving acute myocardial infarction: safety and biochemical effects. *Circulation* 1995; **92:** 2855–62.
2. Šochman J, *et al.* Infarct size limitation: acute N-acetylcysteine defense (ISLAND trial): preliminary analysis and report after the first 30 patients. *Clin Cardiol* 1996; **19:** 94–100.

3. Marchetti G, *et al.* Use of N-acetylcysteine in the management of coronary artery diseases. *Cardiologia* 1999; **44:** 633–7.
4. Sochman J. N-acetylcysteine in acute cardiology: 10 years later: what do we know and what would we like to know?! *J Am Coll Cardiol* 2002; **39:** 1422–8.

Nitrate tolerance. Acetylcysteine appears to be able to potentiate the peripheral and coronary effects of glyceryl trinitrate.[1] While some studies[2-5] have suggested that acetylcysteine can reverse tolerance to nitrates in patients with coronary heart disease or heart failure, others have failed to find any benefit,[6] although there may be a specific subgroup of responders.[5] The various attempts at overcoming nitrate tolerance are discussed on p.1297.

1. Horowitz JD, *et al.* Combined use of nitroglycerin and N-acetylcysteine in the management of unstable angina pectoris. *Circulation* 1988; **77:** 787–94.
2. Packer M, *et al.* Prevention and reversal of nitrate tolerance in patients with congestive heart failure. *N Engl J Med* 1987; **317:** 799–804.
3. May DC, *et al.* In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. *N Engl J Med* 1987; **317:** 805–9.
4. Boesgaard S, *et al.* Preventive administration of intravenous N-acetylcysteine and development of tolerance to isosorbide dinitrate in patients with angina pectoris. *Circulation* 1992; **85:** 143–9.
5. Pizzulli L, *et al.* N-acetylcysteine attenuates nitroglycerin tolerance in patients with angina pectoris and normal left ventricular function. *Am J Cardiol* 1997; **79:** 28–33.
6. Hogan JC, *et al.* Chronic administration of N-acetylcysteine fails to prevent nitrate tolerance in patients with stable angina pectoris. *Br J Clin Pharmacol* 1990; **30:** 573–7.

Poisoning and toxicity. Acetylcysteine has been studied for the potential treatment of many forms of toxicity,[1] but only treatment of acute paracetamol poisoning is widely accepted.

1. Chyka PA, *et al.* Utility of acetylcysteine in treating poisonings and adverse drug reactions. *Drug Safety* 2000; **22:** 123–48.

CARBON TETRACHLORIDE. The treatment of carbon tetrachloride poisoning is discussed on p.2021. Reports suggest that prompt intravenous therapy with acetylcysteine may help to minimise hepatorenal damage in acute poisoning with carbon tetrachloride.[1,2] When added to supportive therapy the initial dosage regimen should be the same as that used for paracetamol poisoning but as carbon tetrachloride has a much longer half-life than paracetamol, the duration of treatment may need to be increased.[3]

1. Ruprah M, *et al.* Acute carbon tetrachloride poisoning in 19 patients: implications for diagnosis and treatment. *Lancet* 1985; **i:** 1027–9.
2. Mathieson PW, *et al.* Survival after massive ingestion of carbon tetrachloride treated by intravenous infusion of acetylcysteine. *Hum Toxicol* 1985; **4:** 627–31.
3. Meredith TJ, *et al.* Diagnosis and treatment of acute poisoning with volatile substances. *Hum Toxicol* 1989; **8:** 277–86.

PARACETAMOL. Acetylcysteine is usually the antidote of choice for paracetamol overdosage (see p.108). The intravenous route is favoured in the UK, despite possible anaphylactic reaction, mainly because of concerns over the effects of vomiting and activated charcoal on oral absorption.[1] In the USA the oral route has conventionally been used, despite the unpleasant odour and taste of acetylcysteine solutions, with no evident reduction in effect by charcoal.[2] The intravenous route is now also licensed in the USA. Oral and intravenous formulations appear to be equally effective.[3] A disadvantage of the oral route is therapeutic failure in those patients who develop nausea and vomiting, which occurs in most patients with severe poisoning; delays in absorption may also be of concern especially when the end of the critical 8-hour interval is approaching. However, with oral doses, the whole absorbed dose passes through the liver, producing high local concentrations at the site of toxicity.[4] Some consider the intravenous route to be more reliable, and to require fewer doses and a shorter duration of treatment.[5] The major disadvantage of intravenous use is possible anaphylactic reaction. Although these reactions are considered uncommon in patients with paracetamol poisoning, rare fatalities have been reported, and patients with asthma appear to be at particular risk (see also above).[4] Some infuse the first dose of acetylcysteine over 60 minutes instead of the recommended 15 minutes[5] in order to reduce the incidence and severity of reactions. However, a multicentre, randomised study found no reduction in adverse outcomes with a 60-minute infusion compared to the standard infusion period of 15 minutes.[6] It has been suggested that intravenous acetylcysteine may be preferred in those patients with severe poisoning, who present late, who have nausea and vomiting, or who have problems with absorption. Oral use might be preferred in those who present early with uncomplicated mild to moderate poisoning, or who have asthma.[4,7] Whichever route is given, the interval is considered the single most important factor for the prevention of severe hepatic damage.[3,4]

1. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; **346:** 547–52.
2. Bowden CA, Krenzelok EP. Clinical applications of commonly used contemporary antidotes: a US perspective. *Drug Safety* 1997; **16:** 9–47.
3. Brok J, *et al.* Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/10/06).
4. Prescott L. Oral or intravenous *N*-acetylcysteine for acetaminophen poisoning? *Ann Emerg Med* 2005; **45:** 409–13.
5. Anonymous. Acetylcysteine (Acetadote) for acetaminophen overdosage. *Med Lett Drugs Ther* 2005; **47:** 70–1.
6. Kerr F, *et al.* The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* 2005; **45:** 402–8.
7. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 2006; **63:** 1821–7.

Respiratory disorders. Acetylcysteine has been used as a mucolytic in a variety of respiratory disorders associated with productive cough (p.1547). Although there is controversy over the benefits of mucolytics in treating chronic bronchitis or chronic obstructive pulmonary disease (COPD), there is some evidence that they may reduce exacerbations (see p.1112). However, a double-blind multicentre study in patients with COPD failed to find evidence that acetylcysteine 600 mg daily by mouth reduced exacerbations;[1] like most other interventions in this condition, it could also not be shown to reduce the rate of decline in lung function.

For the use of aerosolised heparin and acetylcysteine to treat inhalation injury see Burns, above. It has been suggested that intravenous acetylcysteine might also be of use in acute respiratory distress syndrome (ARDS—p.1498),[2] possibly due to its action as a free radical scavenger,[2,3] but controlled studies in established ARDS failed to show benefit.[4,5]

Acetylcysteine has been investigated in idiopathic pulmonary fibrosis (see Diffuse Parenchymal Lung Disease, above). See also above for the use of acetylcysteine in the management of cystic fibrosis.

1. Decramer M, *et al.* Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005; **365:** 1552–60.
2. Bernard GR. Potential of N-acetylcysteine as treatment for the adult respiratory distress syndrome. *Eur Respir J* 1990; **3** (suppl 11): 496S–498S.
3. Skolnick A. Inflammation-mediator blockers may be weapons against sepsis syndrome. *JAMA* 1990; **263:** 930–1.
4. Jepsen S, *et al.* Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992; **20:** 918–23.
5. Domenighetti G, *et al.* Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. *J Crit Care* 1997; **12:** 177–82.

Scleroderma. Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome resulting from scleroderma (see p.1817).

Preparations

BP 2008: Acetylcysteine Injection;
USP 31: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Acetylcysteine Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: AC Lan; ACC†; Acemuk; Fluimucil†; Lubrisec†; ***Austral.:*** Mucomyst; Parvolex; ***Austria:*** ACC; Aeromuc; Aerosolv; Bronchohexal; Bronchoplus; Cimelin; Cimexyl; Fluimucil; Husten ACC; Hustenloser; Mucobene; Mucomyst; NAC; Pulmovent†; Siccoral; ***Belg.:*** Docacetyl; Lysodrop†; Lysomucil; Lysox; Mucomyst; Pectomucil; ***Braz.:*** Bromuc; Flucistein; Fluimucil; Fluimucil Solucao Nasal; NAC; ***Canad.:*** Mucomyst; Parvolex; ***Chile:*** Mucolitico; ***Cz.:*** ACC; Broncholysin†; Fluimucil; L-Cimexyl†; Mucobene; NAC; Solmucol; ***Denm.:*** Alcur†; Granon; Mucolysin; Mucomyst; ***Fin.:*** Mucomyst; Mucoporetta; ***Fr.:*** Broncoclar; Codotussyl Expectorant; Exomuc; Fluimucil; Genac; Humex Expectorant; Mucolator; Mucomyst; Mucomystendo; Mucospire; Solmucol; Tixair; ***Ger.:*** ACC; Acemuc; Acetabs; Acetyst; Atse†; Azubronchin†; Bromuc†; Durabronchal†; Fluimucil; Muciteran†; Muco Sanigen†; Mucocedyl†; Mucret; Myxofat; NAC; Phamuc†; Pulmicret†; Siran†; ***Gr.:*** Chricetyl; Elicor†; Flumil Antidoto; Flustaren†; Kantrenol; Mucomyst; Neocof; Ovoctil†; Parvolex; Saloril†; Spacyl†; Trebon; Vaden†; Vlenolys; ***Hong Kong:*** Exomuc; Fluimucil; Hidonac; Mucolator†; Mutamso; Parvolex; Solmucol; ***Hung.:*** Ac-Pulmin†; ACC; Fluimucil; NAC; Solmucol; Solv-Ac T†; Sputopur; ***India:*** Mucomix; ***Indon.:*** Hidonac; ***Irl.:*** Parvolex; ***Israel:*** Mucomyst†; Reolin; Siran; ***Ital.:*** Altersol; Brunac; Fluimucil; Hidonac; Mucisol; Mucofial; Mucofrin; Mucoxan; Solmucol; Tirocular; Ultraflu; ***Malaysia:*** Acypront†; Fluimucil; Hidonac; Mucolator; Parvolex; ***Mex.:*** ACC; ***Neth.:*** Bisolbruis; Fluimucil; Mucomyst; Solmucol; ***Norw.:*** Bronkyl; Mucomyst; ***NZ:*** Parvolex; ***Philipp.:*** Fluimucil; Hidonac; Solmucol; ***Pol.:*** ACC; Fluimucil; Syntemucol; Tussicom; ***Port.:*** Fluimucil; Flumil; Mucolator; Pulmosal; Tirocular; ***Rus.:*** ACC (АЦЦ); Exomuc (Экзомюк); Fluimucil (Флуимуцил); Muconex (Муконекс); ***S.Afr.:*** ACC; Parvolex; Solmucol; ***Singapore:*** Fluimucil†; Mucoza†; Solmucol†; Spatam; ***Spain:*** Fluimucil; Flumil; Flumil Antidoto; Flumonac; Frenacil; Locomucil†; Mucoaliv; Mucolibex; Solmucol†; ***Swed.:*** Mucomyst; Viskoferm; ***Switz.:*** ACC; Acemucol; Bisolapid†; DemoLibral; Dynamucil; Ecomucyl; Fluimucil; L-Cimexyl; Muco-Mepha; Mucofluid; Mucostop; NeoCitran Expectorant; Robitussin Expectorant; Secresol; Solmucol; ***Thai.:*** Acetin; Flemex-AC; Flucil; Fluimucil; Hidonac; Mucil; Mucocil; Mucotic; Mucoza; Mysoven; NAC; Simucin; ***Turk.:*** Asist; Brunac; Mentopin; Muconex; NAC; Oxxa; ***UK:*** Parvolex; ***USA:*** Acetadote; Mucomyst; Mucosil†.

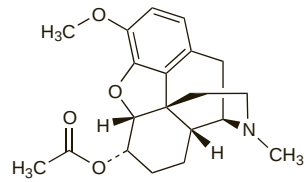
Multi-ingredient: ***Arg.:*** Acemuk Biotic; Fluimucil Biotic†; ***Braz.:*** Rinofluimucil; ***Fr.:*** Rhinofluimucil; ***Ger.:*** Rinofluimucil-S†; ***Hong Kong:*** Rinofluimucil; ***Hung.:*** Rinofluimucil; ***Indon.:*** Dorbigot; Fluimucil; Sistenol; ***Irl.:*** Ilube; ***Ital.:*** Migel; Rinofluimucil; ***Port.:*** Rinofluimucil; ***Rus.:*** Rinofluimucil (Ринофлуимуцил); ***Spain:*** Flumil Antibiotico; Rinoflumil; ***Switz.:*** Rinofluimucil; Solmucaine; Solmucalm; ***Thai.:*** Fluimucil Antibiotic; Rinofluimucil; ***UK:*** Ilube.

Acetyldihydrocodeine Hydrochloride

Acetildihidrocodeína, hidrocloruro de. 4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-yl acetate hydrochloride.

Ацетилдигидрокодеина Гидрохлорид

$C_{20}H_{25}NO_4$,HCl = 379.9.
CAS — 3861-72-1 (acetyldihydrocodeine).
ATC — R05DA12.
ATC Vet — QR05DA12.



(acetyldihydrocodeine)

Profile

Acetyldihydrocodeine hydrochloride is an opioid derivative related to dihydrocodeine (p.48). It is used as a centrally acting cough suppressant for non-productive cough (p.1547) and has been given in a usual oral daily dose of 20 to 50 mg; no more than 20 mg should be taken as a single dose.

Preparations

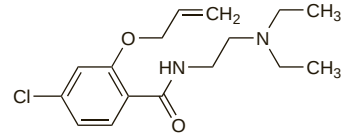
Proprietary Preparations (details are given in Part 3)
Belg.: Acetylcodone.

Alloclamide Hydrochloride *(rINNM)*

Alloclamide, Chlorhydrate d'; Alloclamidi Hydrochloridum; CE-264; Hidrocloruro de aloclamida. 2-Allyloxy-4-chloro-*N*-(2-diethylaminoethyl)benzamide hydrochloride.

Аллокламида Гидрохлорид

$C_{16}H_{23}ClN_2O_2$,HCl = 347.3.
CAS — 5486-77-1 (alloclamide); 5107-01-7 (alloclamide hydrochloride).



(alloclamide)

Profile

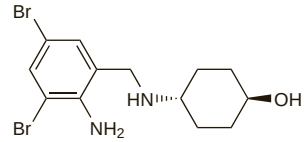
Alloclamide hydrochloride is a cough suppressant.

Ambroxol Hydrochloride *(BANM, rINNM)*

Ambroksolihydrokloridi; Ambroksolio hidrochloridas; Ambroxol, chlorhydrate d'; Ambroxol hydrochlorid; Ambroxol-hidroklorid; Ambroxolhydroklorid; Ambroxoli hydrochloridum; Hidrocloruro de ambroxol; NA-872 (ambroxol). *trans*-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol hydrochloride.

Амброксола Гидрохлорид

$C_{13}H_{18}Br_2N_2O$,HCl = 414.6.
CAS — 18683-91-5 (ambroxol); 15942-05-9 (ambroxol hydrochloride); 23828-92-4 (ambroxol hydrochloride).
ATC — R05CB06.
ATC Vet — QR05CB06.



(ambroxol)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Ambroxol Hydrochloride). A white or yellowish crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Ambroxol is a metabolite of bromhexine (p.1552) and is used similarly as a mucolytic. It is given in a usual oral daily dose of