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†.

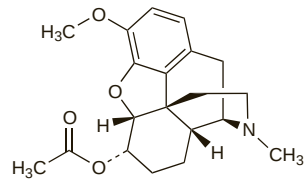
Multi-ingredient: ***Arg.:*** Acemuk Biotic; Fluimucil Biotic†; ***Braz.:*** Rinofluimucil; ***Fr.:*** Rhinofluimucil; ***Ger.:*** Rinofluimucil-S†; ***Hong Kong:*** Rinofluimucil; ***Hung.:*** Rinofluimucil; ***Indon.:*** Dorbigot; Fluimucil; Sistenol; ***Irl.:*** Ilube; ***Ital.:*** Migel; Rinofluimucil; ***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

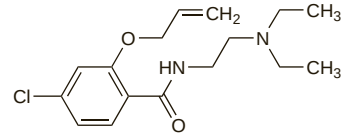
Proprietary Preparations (details are given in Part 3)
Belg.: Acetylcodone.

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

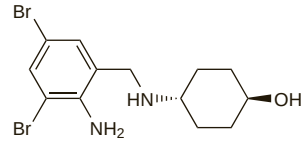
Alloclamide hydrochloride is a cough suppressant.

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