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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; Acetilcistein; Acetylcystein; Acétylcystéine; Acetylcysteinum; Asetilsistein; Asetylikysteini; NSC-111180. N-Acetyl-L-cysteine.

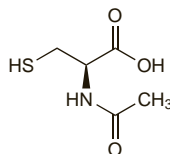
Ацетилацистеин

C₅H₉NO₃S = 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, rINN)

Acetilcisteína sódica; Acétylcystéine Sodique; Natrii Acetylcysteinum.

Натрий Ацетилацистеин

C₅H₈NNaO₃S = 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 and 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 acetyl-

cysteine 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.
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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 patients¹ and severe asthma and respiratory arrest in another² 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 withholding 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. Appelboom 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-acetylcysteine, N,N-diacetylcysteine, 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