Carbocisteine

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Mucus is the first line of defence against harmful pathogens for various epithelia in the body. Mucus acts as a physical barrier against gastrointestinal and respiratory irritants and pathogens. It also contains proteins such as immunoglobulins, glycoproteins, and antimicrobial enzymes (such as lysozyme) that inhibit bacterial growth and biofilm production to protect against infection.[1]

Mucus production is regulated by two mechanisms: the mucus-secreting cells and the mucociliary escalator. In patients with chronic obstructive pulmonary disease (COPD) or asthma, chronic irritation of the airways can lead to mucus hypersecretion, which can overwhelm the mucociliary clearance mechanisms, resulting in excess mucus and the formation of mucus plugs that further reduce clearance. The airways then secrete an excess of inflammatory mediators to clear the obstruction, increasing the viscosity of mucus, resulting in a further decrease in clearance and initiation of inflammation and fibrosis. This cycle invariably results in infection of the static mucus and acute exacerbation of the condition.[1]

Mucolytic agents are used to manage mucus hypersecretion and its sequelae, such as recurrent infections in patients with COPD.[1] Carbocisteine is classified as a classic mucolytic[1] and is thought to reduce the viscosity of secretions by splitting disulphide bonds in mucoproteins.[2] Carbocisteine also increases the volume of sputum, producing an additional expectorative effect.[1] Administration of carbocisteine has been shown to improve sputum fluidity and normalise the bronchial epithelium.[3]

Indications

Carbocisteine is indicated as adjunctive therapy in respiratory tract disorders characterised by excessive viscous mucus in the absence of infection.[4]

Pharmacokinetics

Carbocisteine is rapidly and well absorbed following oral administration of 750 mg, with maximum concentration reached within 77 minutes for the syrup, 120 minutes for tablets and 130 minutes for capsules.[3] Carbocisteine was detected in the mucosa of the ear and paranasal sinuses of healthy subjects following a single dose of 2.7 g and penetrates well into the lung and bronchial secretions.[3,5]

Carbocisteine undergoes partial metabolism in the liver[1] with a diurnal variation resulting in different metabolites forming at different times of the day. Some evidence suggests that higher concentrations of active compounds are achieved with noctur nal administration.[1] Elimination half-life ranges between 90–120 minutes with the different dose forms, and between 30% and 60% of the drug is excreted unchanged in the urine.[1,5]

Dosing

Children (2–5 years)	62.5–125 mg three times daily
Children (5–12 years)	250 mg three times daily
Adults	750 mg three times daily, reducing to 375 mg four times daily when a satisfactory response has been obtained

Efficacy

In a systematic review and meta-analysis by Zeng et al. that included data from four studies involving 1 357 patients:[7]

- There was a decrease in the rate of total number of exacerbations with carbocisteine compared with placebo (-0.43; 95% confidence interval [CI] -0.57, -0.29, $p < 0.01$).
- Carbocisteine improved quality of life (-6.29; 95% CI -9.30, -3.27) and reduced the number of patients with at least one exacerbation (0.86; 95% CI 0.78, 0.95) compared with placebo.
- There was no significant difference in the FEV1 and adverse effects and hospitalisation rate.

The authors concluded that long-term use of carbocisteine (500 mg three times a day) may be associated with lower exacerbation rates, smaller number of patients with at least one exacerbation and higher quality of life for patients with COPD.[7]

A meta-analysis by Cazzola et al. demonstrated that mucolytic drugs effectively protect patients against COPD exacerbations. This beneficial effect was more significant in patients treated for one year or longer. Carbocisteine, erdosteine, and N-acetylcysteine administered at high doses (600 mg twice daily, corresponding to 1 200 mg/day) were the most effective agents.[8]

In the Chinese PEACE study, 709 patients with moderate-to-severe COPD were randomised in a double-blind trial to receive

500 mg carbocisteine (S-carboxymethyl cysteine) or placebo, three times a day for 12 months. Compared to placebo, patients on carbocisteine had a 0.34 mean reduction in exacerbations per patient per year (1.35 vs 1.01, respectively). As measured by the St. George's Respiratory Questionnaire, quality of life was also significantly improved at 12 months in patients taking carbocisteine.[9]

Following an observational, non-interventional, multicentre, cohort study in 501 patients with COPD who were administrated carbocisteine 375 mg (two capsules three times a day for five days, followed by one capsule four times a day for 10 days) and followed up during the next 15 days, carbocisteine was shown to be effective and well-tolerated and improved quality of life in these patients.[10]

Safety

Contraindications

Carbocisteine should not be administered to patients with active gastric ulceration.[4]

Special warnings and precautions for use

Caution is recommended in the elderly, those with a history of gastroduodenal ulcers, or those taking concomitant medications known to cause gastrointestinal bleeding. If gastrointestinal bleeding occurs, patients should discontinue the medication.[6]

Carbocisteine syrup contains sucrose that may affect glycaemic control in patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take carbocisteine syrup.[4,6]

Adverse effects

Gastrointestinal discomfort, nausea, vomiting, diarrhoea, heartburn, gastric ulceration, and gastritis have been reported after the administration of carbocisteine.[3,4,6] Other side effects may include headache, dizziness, and palpitations.[4] Gastrointestinal bleeding, skin rash and fixed drug eruptions may occur rarely.[1,4]

Drug interactions

There are no known interactions with other medicinal products.[4,6]

Important prescribing points

- Mucolytics may be beneficial in selected cases with chronic, tenacious sputum production.
- Sufficient hydration is vital to reducing sputum viscosity.[2]
- Suppression of a productive cough is not recommended as this may cause mucus retention, promote stasis, and encourage the development of infection.[2]

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