Acetylcysteine, a new treatment for an old foe?

Patient

An 80-year-old non-smoking male presents to a community hospital with a 1-month history of progressive dyspnea and hypoxemia requiring supplemental oxygenation to maintain pulse oxymetry at 90%. He does not respond to treatment for heart failure and is transferred for further evaluation. His exam at this time reveals tachypnea, unchanged supplemental oxygen requirements, and bibasilar “Velcro-like” crackles. High resolution CT scan of the thorax shows basilar honeycombing and traction bronchiectasis most consistent with idiopathic pulmonary fibrosis (IPF).

Clinical Question

In a patient with idiopathic pulmonary fibrosis, does N-acetylcysteine decrease dyspnea or mortality?

Search Strategy

1. Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE) using OVID interface (searched April 2006)
   a) “Acetylcysteine” or “mucomyst” or “NAC”
   b) “Pulmonary fibrosis”
   c) Combine (a) and (b)
      i. No applicable results found
2. All years of MEDLINE (1966-April 2006) using OVID interface
   a) “Pulmonary fibrosis” (MeSH heading)
   b) “Acetylcysteine” (MeSH heading)
   c) Combine (a) and (b) limit to humans and English language
      i. 18 studies
      ii. Demedts et al, specifically addresses N-acetylcysteine use in IPF—High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

Study Characteristics

- Multinational, double blind, randomized control trial.
- 182 patients, aged 18-75 with a negative bronchial-alveolar lavage and histologic or CT scan evidence of usual interstitial pneumonitis (UIP) otherwise referred to as idiopathic pulmonary fibrosis (IPF).
- Inclusion criteria
  - Minimum of 3 months of disease
  - Vital capacity of ≥80% predicted
  - Total lung capacity of ≤90% predicted
  - Diffusion capacity of <80% predicted
  - Dyspnea
- Intervention
  - 600mg N-acetylcysteine orally 3 times daily versus matched placebo.
  - All patients received a weight adjusted prednisone taper and azathioprine 2mg/kg/day.
- Primary end points: At 12 months.
  - Change in vital capacity (VC).
  - Change in diffusion capacity (DLco).
- Secondary end points: clinical, radiologic, physiologic score; dyspnea score; maximum exercise indexes; oxygen uptake; high-resolution CT scores; health status (St. George’s Respiratory Score).

Validity of Evidence

- Properly randomized trial with centrally performed, computer generated randomization.
- Intention to treat analysis was used.
- Patients were followed for a total of 12 months with regular clinical exams, labs and imaging.
  - Adequate time to detect functional deterioration in patients with UIP.
- Dropout rate plus death rate was approximately 30% in both the study drug and placebo groups.
- The last observation was carried forward.
- Patients, clinicians and study personnel were appropriately blinded.
- The groups were similar at the study’s start and appeared to be treated equally except for N-acetylcysteine use.
- Overall this study is of good methodological quality, but has potential bias due to the high drop-out rate.

Results

- Modest improvement in VC and DLco.
  - VC mean difference 9% or 0.18 L (CI=0.03-0.32).
  - DLco mean difference 24% or 0.75 mmol/min/kPa (CI=0.27-1.23).
- No significant effect on dyspnea score, health status, or any other secondary endpoints.
- No significant difference in adverse events except a decrease in bone marrow toxicity in the N-acetylcysteine group.

Applying the Evidence to the Patient

- The patient would likely meet inclusion criteria for this study.
- The treatment is feasible and has few side effects.
- Potential benefit of N-acetylcysteine is a slowing of deterioration of VC and DLco.
- Unknown if this has any effect on dyspnea or mortality.
- Potential harms include increased cost, inconvenience, and difficulty with long term compliance.

Summary

This is a small, good quality, randomized controlled trial that shows a modest slowing in the deterioration of VC and DLco with the addition of high dose N-acetylcysteine to standard therapy in IPF. Overall the study should be interpreted with caution given its high drop out rate, which may have biased the results towards a more dramatic slowing of the disease progression. There were no differences in dyspnea score or functional status. There was no increase in the adverse events in the N-acetylcysteine group and the medication is inexpensive. Given only modest effects of N-acetylcysteine on VC and DLco, no change in functional scores, and the flaws of the study we would hesitate to use N-acetylcysteine as standard therapy in all patients with IPF.

Bottom Line

High dose N-acetylcysteine may result in a modest slowing in the deterioration of the surrogate markers (VC and DLco). Based on the results of this study, exactly how N-acetylcysteine will impact patients’ quality of life and long term mortality is unclear, hence we would not routinely recommend it at this time. Further research is needed.

Reference:
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