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Abbreviated Drug Evaluation: Hypertonic Saline Inhalation for Cystic Fibrosis

Month/Year of Review: September 2012
End date of literature search: August 2012
Generic Name: Hypertonic Saline
PDL Class: None

Research Questions:

- Is there evidence to support the use of inhaled hypertonic saline (HS) in cystic fibrosis (CF)?
- Are there certain subpopulations in which inhaled HS has a clinical advantage in efficacy or safety?

Conclusions:

- Based on fair quality evidence and a moderate estimated benefit (mean change in forced expiratory volume at one second [Fev1] of 3%-7.7%), current guidelines recommend the chronic use of inhaled HS for patients six years of age and older to improve lung function and reduce exacerbations.
- There is moderate quality evidence that treatment with HS in CF patients improves short term lung function, decreases pulmonary exacerbations, and has a small effect on improvement in quality of life.
- There is insufficient evidence to determine the long term improvement in lung function from inhaled HS.
- There is low quality evidence that in infants and young children, there is no difference in the rate of pulmonary exacerbations with HS compared to isotonic saline.
- Inhaled HS is relatively well tolerated with cough and bronchospasm being the most common adverse events.
- There is insufficient evidence to determine the long term effects of HS on mortality in patients with CF.

Recommendations:

- Include inhaled hypertonic saline in the CF medication class.
- Due to evidence of improved short term lung function and reduction in pulmonary exacerbations, make preferred for patients greater than six years of age and evaluate comparative costs within the class.

Background:

Cystic Fibrosis (CF) is characterized by retained dry thick mucus that provides a source for chronic infection. Mucolytics are first-line therapy because the thick mucus is the primary cause for airway obstruction, including both dornase alfa and inhalations of HS.[1] In the lungs, dysfunction of the CF Transmembrane Conductance Regulator (CFTR) gene causes airway surface liquid (ASL) depletion and thickened viscous mucus results in decreased mucociliary clearance (MCC). Inhaled HS induces osmotic flow of water into the mucus layer resulting in improved mucus run, transportability of sputum, and increased hydration of the airway surface. HS has been shown to improve lung function and reduce exacerbation rates in patients with CF.

Twice daily inhalation of has been shown to reduce sputum markers of inflammation, reduce the risk of pulmonary exacerbation, and modestly improve pulmonary function.[2] The primary limitation of HS is poor tolerance due to increased cough and bronchopasm, as well as the time it takes for administration.[2,3] Also, the benefit of HS occurs early and many trials evaluating HS have relatively small numbers and of short duration.[2,3]

Guidelines:

The 2007 Cystic Fibrosis Foundation Pulmonary Guidance outlines the treatment recommendations for chronic maintenance of lung health in CF patients. Using the U.S. Preventive Services Task Force recommendation grades, chronic treatments are given an evidence grade as well as an estimated treatment effect. The guidelines determined the evidence for the use of HS in patients with CF to be of fair quality (two randomized controlled trials, two randomized crossover trials vs. dornase alfa). Studies demonstrated it was well tolerated in general and the most common side effect was cough or bronchospasm. A review of the literature demonstrated that HS therapy resulted in a mean increase in FEV1 of 15% compared with 2.8% in the placebo group (normal saline). Only one study was identified which evaluated HS on pulmonary exacerbations and found that HS demonstrated a 56% reduction in pulmonary exacerbations for patients receiving 7% saline compared with normal saline. The committee concluded that HS provided a net benefit that was moderate. For patients 6 years of age and older with CF , the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations (fair level of evidence, grade of recommendation B).[4]

Clinical Efficacy:

Systematic Reviews

The Cochrane Collaboration conducted a systematic review in 2010 to investigate the effects of treatment with nebulised HS in CF compared to placebo and or other treatments for mucociliary clearance. A total of 19 trials were identified, but only 12 trials met the inclusion criteria with a total of 442 participants (aged 6 years to 46 years).[3] Results demonstrated that while the use of hypertonic saline has been shown to lead to a small improvement in lung function up to four weeks of treatment, this effect was not sustained at 48 weeks. It was shown to reduce the frequency of pulmonary exacerbations and may have a small effect on improvement in quality of life in adults. [3]

Seven trials, including 281 patients, compared hypertonic saline 3% to 7% versus isotonic saline. The data from the trials were pooled and analyzed. There was a significant improvement in mean percent change in FEV1 after 4 weeks of treatment with hypertonic saline 3-7% compared to isotonic saline, (MD 4.15; 95% CI 1.14 to 7.16). There was also a significant improvement in forced vital capacity (FVC) at four weeks (MD 2.75; 95% CI 0.00 to 5.49). There was no significant difference in FEV1 and FVC demonstrated at 48 weeks. The mean number of exacerbations per participant in the control group was 0.89, as compared with 0.39 in the hypertonic saline group (difference, 0.50, 95% CI 0.14 to 0.86; P =0.02). The meta-analysis of the data demonstrated a significant improvement in quality of life, as measured by the Cystic Fibrosis questionnaire; or CFQ (MD 7.77; 95% CI 1.86 to 13.68) with hypertonic saline compared to the control group. [3] Three

trials, including 80 patients, compared hypertonic saline to dornase alfa. After three months one trial found that dornase alfa led to a greater increase in FEV1 compared to hypertonic saline (MD 8.00%; 95%CI 2.00%to 14.00%).[3]

Clinical Trials

Recently, a fair quality, large, randomized, placebo-controlled study evaluated the use of HS (n=158) compared to isotonic saline (n=163) in children less than six years of age with CF over 48 weeks.[5] This is the first clinical trial assessing chronic HS use in patients less than 6 years of age. Results failed to demonstrate a reduction in the rate of pulmonary exacerbations. Mean age of subjects was 2.2 years and the majority of patients were male. Fifteen participants (9%) withdrew from the HS group compared to 14 (7%) in the isotonic saline group. The pulmonary exacerbation rate was 2.3 (95% CI 2.0-2.5) per person-year in those randomized to HS and 2.3 (95% CI 2.1-2.6) per person-year among those randomized to isotonic saline (ratio of HS compared to isotonic saline 0.97; 95% CI 0.83-1.13). [5] The ratio of mean total days of antibiotic days in HS compared to isotonic saline was 1.13 (95% CI 0.91-1.40). [5] There was also no significant difference in any secondary outcomes (height, weight, respiratory rate, oxygen saturation, and cough). The most common serious adverse event in both groups was cough or increased cough (8% HS vs. 10% isotonic saline). Authors noted that using the outcome of pulmonary exacerbation in younger children may pose a challenge because they presumably have less underlying lung disease than older patients and different endpoints should be evaluated in these younger patients.[6]

References:

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2. Flume PA, Van Devanter DR. State of progress in treating cystic fibrosis respiratory disease. *BMC Med*. 2012;10(1):88.

3. Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database of Systematic Reviews*. 2009;(2). Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001506.pub3/abstract. Accessed July 10, 2012.

4. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am. J. Respir. Crit. Care Med.* 2007;176(10):957–969.

5. Rosenfeld M, Ratjen F, Brumback L, et al. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA*. 2012;307(21):2269–2277.

6. Dasenbrook EC, Konstan MW. Inhaled hypertonic saline in infants and young children with cystic fibrosis. *JAMA*. 2012;307(21):2316–2317.