Cystic fibrosis

Hypertonic saline inhalation in cystic fibrosis—salt in the wound, or sweet success?

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A large-scale study has put hypertonic saline back in the spotlight

Among the greatest challenges facing the cystic fibrosis community at present is the apparently simple task of determining whether a treatment is beneficial or not. Most of the traditional outcome measures may no longer be useful—the outlook for cystic fibrosis has improved so dramatically that using survival is impractical; clinical scoring systems such as the Shwachman-Kulczycki score are too subjective and insensitive,[1] and many children have no respiratory symptoms with pulmonary function within the normal range. The vast majority of patients with cystic fibrosis succumb to terminal respiratory failure, and pulmonary function is strongly predictive of survival.[2] Consequently attention has concentrated on respiratory outcomes, most notably pulmonary function and pulmonary exacerbations. There is however considerable inherent variability in measurements of pulmonary function in cystic fibrosis. The standard measure of pulmonary function is the forced expiratory volume in one second (FEV1), but a change of 10% can be within normal variation.[3] There remains no standard definition of a pulmonary exacerbation, although a number of models have been proposed[4–6]

The popularity of hypertonic saline in cystic fibrosis increased on the basis of small uncontrolled trials,[7–9] and then waned following a large controlled study that reported little effect on pulmonary function.[10] However a recent large-scale study has catapulted it back into the limelight,[11] with extensive coverage in the lay press. It is in this context that we must try to interpret the evidence for or against the use of hypertonic saline in cystic fibrosis.

MODE OF ACTION AND EVIDENCE FOR USE

Cystic fibrosis is a multi-system disorder, caused by mutations in the cystic fibrosis gene. The cystic fibrosis gene encodes for a c-AMP mediated chloride channel known as cystic fibrosis transmembrane conductance regulator (CFTR). In the airway, the defective CFTR leads to abnormal chloride and sodium transport across the epithelium, although there has been controversy over how the defective ion transport resulted in the lung disease observed in cystic fibrosis. There is now increasing evidence for the isotonic "volume" hypothesis which proposes that defective CFTR leads to excessive absorption of fluid from the airway surface layer (ASL), resulting in a lower ASL volume of normal tonicity. The lower ASL volume leads to impaired mucociliary clearance, with retained mucus acting as a focus for infection. The volume hypothesis would predict that strategies that increase the ASL volume will result in increased mucociliary clearance, and thus decreased lung disease.

In vitro hypertonic saline increases the ASL height[12] in an epithelial cell line model. In vivo hypertonic saline increases the mucociliary clearance of radiolabelled aerosol in both normal controls and asthmatics.[13] In cystic fibrosis, hypertonic saline increases mucociliary clearance[8 9 12] for at least eight hours in a dose dependent manner, and increases sputum expectoration.[7] Short term studies over one month show significant increases in FEV1 of up to 12%,[14] and decreased symptoms.[7] However when compared to nebulised recombinant DNase (rhDNase), hypertonic saline did not appear as effective. In an open cross-over comparison of 12 weeks daily nebulised rhDNase (2.5 mg), 12 weeks alternate day rhDNase and 12 weeks 7% hypertonic saline, rhDNase resulted in significantly increased improvements in FEV1 compared to 7% hypertonic saline (16% and 14% *v* 3%).[10] There was no difference in the rate of pulmonary exacerbations between the three treatments, although the numbers were small. It is also noteworthy that there were some children who had greater benefit on hypertonic saline than rhDNase, highlighting the need for individual assessment of response. Subsequently the Cochrane systematic review of inhaled hyperosmolar agents for cystic fibrosis concluded that "there is insufficient evidence to support the use of hypertonic saline as routine treatment for people with cystic fibrosis".[14]

In contrast a recent Australian study reported by Elkins showed significant benefit for hypertonic saline.[11] In a 48-week parallel group study, 164 cystic fibrosis patients were randomised to receive either 5 ml of 7% hypertonic saline or placebo via a nebuliser. All subjects received salbutamol before each treatment. The study was blinded through the addition of quinine sulphate to each treatment as a taste masking agent, and the groups were balanced for age, FEV1, cystic fibrosis centre, physiotherapy and use of rhDNase. After the first month, FEV1 was approximately 3% higher in the hypertonic saline group, and this difference persisted until the end of the study. Although there was no significant difference in the primary outcome—the slope of decline in pulmonary function over the 48 weeks, the averaged FEV1 was significantly higher in the hypertonic saline group.

Two definitions of a respiratory exacerbation were used based on previously described criteria.[4] A severe exacerbation required a combination of four out of 12 clinical signs and symptoms, and the need for intravenous antibiotics. A milder exacerbation required only the presence of four signs or symptoms. The number exacerbations was halved in those receiving hypertonic saline, from 0.89 to 0.39 severe exacerbations/year, and from 2.74 to 1.32 mild exacerbations/year, both significant differences. Furthermore there were significant decreases in the days of antibiotics received per year, and the number of days absent from work or school, both being decreased by two thirds in those receiving hypertonic saline. There were also significant benefits in measures of quality of life. A number of questions remain.

ARE THE FINDINGS APPLICABLE TO OUR PRACTICE?

The study population differed from many cystic fibrosis clinics in Europe, as despite almost 80% of subjects being infected by pseudomonas aeruginosa, fewer than 20% were receiving regular inhaled antibiotics. Similarly few patients were receiving regular oral antibiotics (including azithromycin), and intriguingly there was no significant decline in pulmonary function in either the hypertonic saline or placebo group over the study period. Of note is that hypertonic saline appeared equally efficacious in those receiving concomitant nebulised rhDNase or tobramycin, and showed a significantly greater effect in those receiving regular oral antibiotics

Hypertonic saline induces coughing, and indeed is used as an agent for inducing sputum in a number of respiratory conditions including cystic fibrosis. There is a perception that the primary mode of action of hypertonic saline is through induced coughing, and that this decreases its tolerability to patients. Yet the increased mucociliary clearance in cystic fibrosis is independent of coughing, and a pooling of all the studies to date estimates that less than 8% of patients are unable to tolerate hypertonic saline because of local side effects such as cough or chest tightness if bronchodilators are administered beforehand (MR Elkins presentation to the European Cystic Fibrosis Society (ECFS), Copenhagen 16/6/6). In the Elkins study the immediate symptoms settled after a mean of eight doses, and reported compliance with therapy was slightly higher in the hypertonic saline arm.

HOW DOES HYPERTONIC SALINE COMPARE WITH OTHER TREATMENTS?

Comparisons are difficult due to different designs and outcomes, but the effect on respiratory exacerbations appears greater than daily rhDNase,[4 15] which decreases exacerbations by a third, and alternate month inhaled tobramycin which decreases exacerbations by at best a quarter.[16 17] The only treatment modality that appears at least equivalent is regular oral azithromycin, which also halves the number of courses of intravenous antibiotics.[18–20]

WHAT IS THE OPTIMAL DOSING FOR HYPERTONIC SALINE?

There appears little benefit for using concentrations above 7%,[9] but there might be benefit from increasing doses. In the short term, nebulising 10 ml of 7% hypertonic saline twice daily results in the greatest increase in FEV1 (12%),[14] but nebulisation times were up to 84 minutes per day[21]—a potentially unacceptable treatment load. Nebulising 4–5 ml twice daily results in a 3% increase in FEV1, with nebulisation times of approximately 40 minutes per day,[10 11] in addition to the already burdensome treatment regime for cystic fibrosis. However at the recent ECFS meeting, Elkins presented data for equivalent effects for rapid delivery of hypertonic saline via the eFlow electronic nebuliser (MR Elkins presentation to ECFS, Copenhagen 16/6/6), offering the possibility of therapeutic benefit with acceptable treatment burden.

WHAT IS AN IMPORTANT OUTCOME MEASURE IN CYSTIC FIBROSIS?

There is an interesting parallel between cystic fibrosis trials and asthma trials, where there has been a marked shift away from measures of pulmonary function such as FEV1 or peak flow variability, towards measures of greater relevance to the patient such as exacerbation rate and quality of life measures.[22] Although FEV1 is strongly predictive of two-year survival in cystic fibrosis, it is likely that the rate of decline in pulmonary function, or exacerbation rate is of greater long term importance. Donladson has speculated[12] that hypertonic saline has only a modest effect on FEV1 because it is unable to penetrate obstructed airways, but in unobstructed airways it increases mucociliary clearance to remove exogenous agents that might precipitate an exacerbation. Recently Saiman and colleagues re-analysed their controlled trial of azithromycin in cystic fibrosis patients, and demonstrated that benefits in exacerbation rate were independent of change in FEV1.[23]

WHO SHOULD RECEIVE HYPERTONIC SALINE?

The additional treatment burden of hypertonic saline via conventional nebulisers probably precludes its widespread introduction. However with the possibility of rapid delivery systems and shorter delivery times, in future it might be better to ask who should *not* try hypertonic saline. In a health system under massive financial strain, hypertonic saline is cheap (less than £0.50 per day), does not need cold storage, and appears safe. What it lacks is the benefit of a large-scale pharmaceutical marketing budget. Thus with new delivery systems it may be reasonable to try most patients on HS, even if some will be unable to tolerate its effects. All patients should receive an inhaled bronchodilator prior to administering hypertonic saline. It is unlikely to replace existing therapies, as the benefits appear independent of concurrent medication. Judging benefit in an individual patient will remain problematic.

If the volume hypothesis for the pathogenesis of cystic fibrosis is correct, and hypertonic saline acts by inducing a fluid flux to increase the volume of ASL, it is potentially the first treatment of the cystic fibrosis lung that acts on the underlying mechanism rather than downstream inflammation (Azithromycin, rhDNase) or infection (tobramycin or colistin). There is an urgent need for studies in young infants, ideally detected early by newborn screening. It also opens the possibility of other agents that increase fluid in the ASL, such as mannitol or the $P2Y_2$ receptor agonist Denufosol tetrasodium.[24] The sugar alcohol mannitol in particular is attractive as it also increases bronchial clearance in cystic fibrosis,[25] and in a small study has been demonstrated to significantly increase FEV1.[26] There is currently an Australian/UK multicentre study of regular inhaled mannitol ongoing (http://clinicaltrials.gov/ study no NCT00117208). So the future treatment of cystic fibrosis might be salt and sugar.

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REFERENCES

1 **Hafen GM**, Ranganathan SC, Robertson CF, *et al.* Clinical scoring systems in cystic fibrosis. *Pediatr Pulmonol* 2006;**41**:602–17.
2 **Kerem E**, Reisman J, Corey M, *et al.* Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;**326**:1187–91.
3 **Cooper PJ**, Robertson CF, Hudson IL, *et al.* Variability of pulmonary function tests in cystic fibrosis. *Pediatr Pulmonol* 1990;**8**:16–22.
4 **Fuchs HJ**, Borowitz DS, Christiansen DH, *et al.* Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994;**331**:637–42.
5 **Rosenfeld M**, Emerson J, Williams-Warren J, *et al.* Defining a pulmonary exacerbation in cystic fibrosis. *J Pediatr* 2001;**139**:359–65.
6 **Eng PA**, Morton J, Douglass JA, *et al.* Robertson CF Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. *Pediatr Pulmonol* 1996;**21**:77–83.
7 **Rabin HR**, Butler SM, Wohl MEB, *et al.* Pulmonary exacerbations in cystic fibrosis. *Pediatr Pulmonol* 2004;**37**:400–406.
8 **Robinson M**, Regnis JA, Bailey DL, *et al.* Effect of hypertonic saline, amiloride, and cough on mucociliary clearance in patients with cystic fibrosis. *Am J Respir Crit Care Med* 1996;**153**:1503–9.
9 **Robinson M**, Hemming AL, Regnis JA, *et al.* Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. *Thorax* 1997;**52**:900–3.
10 **Suri R**, Metcalfe C, Lees B, *et al.* Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial. *Lancet* 2001;**358**:1316–21.
11 **Elkins MR**, Robinson M, Rose BR, et al; National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;**354**:229–40.
12 **Donaldson SH**, Bennett WD, Zeman KL, *et al.* Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med* 2006;**354**:241–50.
13 **Daviskas E**, Anderson SD, Gonda I, *et al.* Inhalation of hypertonic saline aerosol enhances mucociliary clearance in asthmatic and healthy subjects. *Eur Respir J* 1996;**9**:725–32.
14 **Wark PA**, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev* 2005;**20**:CD001506.
15 **Quan JM**, Tiddens HA, Sy JP, et al; Pulmozyme Early Intervention Trial Study Group. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001;**139**:813–20.
16 **Ramsey BW**, Pepe MS, Quan JM, *et al.* Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;**340**:23–30.
17 **Moss RB**. Long term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. *Chest* 2002;**121**:55–63.
18 **Wolter J**, Seeney S, Bell S, *et al.* Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax* 2002;**57**:212–16.
19 **Saiman L**, Marshall BC, Mayer-Hamblett N, et al; Macrolide Study Group. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA* 2003;**290**:1749–56.
20 **Clement A**, Tamalet A, Le Roux E, *et al.* Long term effects of azithromycin in patients with cystic fibrosis: a double-blind, placebo-controlled trial. *Thorax* 2006;**61**:895–902.
21 **Ballmann M**, von der Hardt H. Hypertonic saline and recombinant DNase: a randomised cross-over pilot study in patients with cystic fibrosis. *J Cyst Fibrosis* 2002;**1**:35–37.
22 **Pauwels RA**, Lofdahl CG, Postma DS, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;**337**:1405–11.
23 **Saiman L**, Mayer-Hamblett N, Campbell P, et al; Macrolide Study Group Heterogeneity of treatment response to azithromycin in patients with cystic fibrosis. *Am J Respir Crit Care Med* 2005;**172**:1008–12.
24 **Deterding R**, Retsch-Bogart G, Milgram L, *et al.* Cystic Fibrosis Foundation Therapeutics Development Network. Safety and tolerability of denufosol tetrasodium inhalation solution, a novel P2Y2 receptor agonist: results of a phase 1/phase 2 multicenter study in mild to moderate cystic fibrosis, *Pediatr Pulmonol* 2005;**39**:339–48.
25 **Wills P**, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. *Cochrane Database Syst Rev* 2006;**2**:CD002996.
26 **Charlton B**, Lassig A. Inhaled dry powder mannitol (bronchitol) improves FEV1 in cystic fibrosis. *J Cyst Fibrosis* 2006;**5**(Suppl 1):S11.