Inhaled medication other than antibiotics

Chronic use of inhaled hypertonic saline

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Background

Defects in CFTR protein function impact either upon cAMP-dependent chloride secretion or in increased epithelial sodium channel (ENaC) mediated ion absorption in the superficial airway epithelium; the increased water reabsorption across airway epithelial cells leads to dehydration of the airway surface liquid layer, stasis of thickened mucus, and airways obstruction. Dehydration of the airway surface liquid layer has been implicated as the primary initiating event in CF-related lung disease and therapeutic interventions to improve mucus clearance is a cornerstone of treatment in CF.

Hypertonic saline (HS) may represent a potential alternative or supplementary therapy to improve mucociliary clearance (Trimble AT, 2018). In the long term the improvement in mucociliary function may reduce bacterial load and chronic inflammation within the airways and therefore reduce the decline in lung function that is consequent to this. HS is easy to administer and inexpensive.

HS is defined as a solution possessing an osmotic pressure greater than that of physiologic isotonic salt solution (0.9% NaCl). Several mechanisms have been proposed for the observed effectiveness including changes in the rheological characteristics of the airway mucus, increasing airway surface liquid hydration, inhibition of ENaC, as well as immunomodulatory effects.

For reviews on HS read Reeves EP, 2015, Southern KW, 2019 and Terlizzi V, 2021.

Based on the available evidence HS has been recommended in Cystic Fibrosis Foundation Guidelines (Mogayzel Jr. PJ, 2013) as a standard of treatment for children 6 years and above and in the standards of care of the European CF Society (Castellani C, 2018).

In spite of these recommendations, the use of HS is very different in the different countries. In The US, the CFF Patient Registry reports in 2019 that 74.6% of patients > 6 years of age use HS. In Europe, the range of patients using HS is very wide, from 34% in the UK, to 80% in Germany and 44% in Italy.

A study, using national registry data, comparing longitudinal lung function in children with CF in the USA and UK showed that US children homozygous for F508del had better lung function than UK children. This difference was mainly linked to differences in the use of early treatments as dornase alfa and HS (Schluter DK, 2022)

A systematic review and meta-analysis by Ullah SE et al (Ullah SE, 2023), after examining 7 studies (n = 390 subjects) states that treatment with HS in younger children with CF improves lung clearance, symptoms and quality of life. FEF_{25-75} may prove a more sensitive measure for assessing intervention related improvements in pediatric CF trials.

Issues

1. To determine whether there is evidence of benefit in using HS in people with CF in terms of a reduction in morbidity or mortality and in terms of improvement of lung function
2. To identify any adverse event associated with the use of HS
3. To evaluate the cost of use of HS
4. To compare the efficacy of HS with other mucolytics
5. To determine the effect of timing of HS inhalation on measures of clinical efficacy in people with cystic fibrosis (in relation to airway clearance techniques or time of the day)
6. To determine the effect of HS on CF sinonasal disease
7. To compare the aerosol characteristics of HS delivered by nebulizers of different operating principles.
8. To evaluate the effect of withdrawing HS or other mucolytics

What is known

Regarding issue 1

HS was shown to reduce the frequency of pulmonary exacerbations, to have a small effect on improvement in quality of life in adults and, in concentrations of 5% to 7%, to improve mucociliary clearance (MCC), although not in all the patients. Age of patients could be a relevant factor varying the clinical response: a large RCT (48-week study of inhaled hypertonic saline in children with CF under six years of age) failed to demonstrate a treatment-related reduction in the rate of pulmonary exacerbation in this cohort of patients (Rosenfeld M, 2012). A substudy derived from this trial showed that Lung Clearance Index (a noninvasive measure of ventilation inhomogeneity that holds promise as an objective physiologic endpoint for clinical trials in infants and preschool children with CF) improved in the HS group and remained stable in the isotonic saline group (Subbarao P, 2013).

A recent RCT (Dentice RL, 2016) showed that addition of HS to the management of a CF exacerbation did not reduce the length of hospital stay, although HS speeded the resolution of exacerbation symptoms and allowed patients to leave hospital with greater symptom resolution.

A crossover, randomized clinical (Nenna R, 2017) trial evaluated the effects of inhaled hypertonic (7%) saline on lung function test in preschool children with cystic fibrosis. After a 16-weeks treatment with HS an improvement of FVC (p=0.02) and a favorable trend of FEV1 were registered. A worsening of FEV1 (p<0.0001) and of FEF25-75 (p=0.019) were found in NS group. No differences were found in expiratory and inspiratory Rint in both groups. No serious adverse events occurred. This RCT had, however, some methodological problem.

Little evidence is available that HS leads to an improvement in lung function in the long term. Recently an observational study with a mean follow up of 39.7 months (Ellemunter H, 2016) showed a significant improvement of ventilation inhomogeneity after the start of HS therapy.

Evidence that inhaled HS enhances mucociliary clearance, improves lung function, and reduces pulmonary exacerbations are available especially in people with CF older than age 6 years. German researchers studied feasibility, safety and efficacy of preventive inhalation with HS compared to isotonic saline (IS) in infants with CF including LCI and MRI as outcome measures (Stahl M, 2019). In this RCT 42 infants with CF less than 4 months of age were randomized to twice daily inhalation of 6% HS or 0.9% IS for 52 weeks. Inhalation with HS was safe and well tolerated, and resulted in improvements in LCI and weight gain in infants with CF.

Canadian and US researchers assessed the effect of inhaled HS on the lung clearance index ($LCI_{2·5}$)-a measure of ventilation inhomogeneity-in children aged 3-6 years with CF, using IS as a comparator (SHIP study, Saline Hypertonic in Preschoolers) (Ratjen F, 2019). At 48 weeks, treatment with HS was associated with a significant decrease (ie, improvement) in $LCI_{2·5}$ compared with IS (mean treatment effect -0·63 $LCI_{2·5}$ units [95% CI -1·10 to -0·15]; p=0·010). In conclusion, inhaled HS improved the $LCI_{2·5}$ in children aged 3-6 years, and could be a suitable early intervention in cystic fibrosis. This study was followed by a further evaluation (SHIP-CT study), aiming to assess the effect of inhaled HS on chest CT imaging in children aged 3–6 years with CF. Inhaled HS for 48 weeks had a positive effect also on structural lung changes in children aged 3–6 years with CF relative to IS (Tiddens HAWM, 2022). On this basis, an algorithm was developed and validated to automatically measure bronchus and artery (BA) dimensions of BA-pairs on chest CT. Aim of the study was to assess the effect of HS on bronchial wall thickening and bronchial widening using the BA-analysis. The automatic BA-analysis showed a positive impact of inhaled HS on bronchial lumen and wall thickness, but no treatment effect on progression of bronchial widening over 48 weeks (Chen Y, 2023).

In 2020, US researchers (Donaldson SH, 2020) performed a randomized, placebo controlled, double blind study of 6% versus 0.12% sodium chloride, delivered three-times daily with an eFlow nebulizer for 4 weeks. MCC was measured using gamma scintigraphy at baseline, 2-hours after the first study treatment, and ~12-hours after the final dose (at day 28). Spirometry, respiratory symptoms (CFQ-R), and safety were also assessed. Study treatments were generally well tolerated and safe. HS (6% sodium chloride) resulted in a significant, sustained improvement from baseline in whole lung clearance after 4 weeks of therapy (p = 0.014).Improvements in spirometry with HS did not reach statistical significance but correlated with MCC changes.

In 2023, literature was reviewed by a CDSR (Wark P, 2023). The authors conclude that they are very uncertain if regular use of nebulised hypertonic saline by adults and children over the age of 12 years with CF results in an improvement in lung function after four weeks (three trials; very low-certainty evidence); there was no difference seen at 48 weeks (one trial; low-certainty evidence). Hypertonic saline improved LCI modestly in children under the age of six years. Evidence from one small cross-over trial in children indicates that rhDNase may lead to better lung function than hypertonic saline at three months; qualifying this, the authors highlight that while the study did demonstrate that the improvement in FEV_1 was greater with daily rhDNase, there were no differences seen in any of the secondary outcomes. Hypertonic saline does appear to be an effective adjunct to physiotherapy during acute exacerbations of lung disease in adults. However, for the outcomes assessed, the certainty of the evidence ranged from very low to low at best, according to the GRADE criteria. Finally, the role of hypertonic saline in conjunction with cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy now needs to be considered, and future research needs to focus on this aspect.

Regarding issues 2-3

When delivered following a bronchodilator it appears to be an inexpensive and safe additional therapy for people with CF.

The use of a formula containing 7% HS and 0.1% hyaluronic acid (HA) [basing its use on the protective effects of HA against elastin injury and on a greater ease of administration (i.e., the perceived acceptability of inhalation)], showed no significant differences in the prevalence of moderate/severe symptoms of cough, saltiness, and throat irritation in pulmonary functions tests after 28 days (Brivio A, 2016).

In people with cystic fibrosis (pwCF), regular nebulisation of 6% or 7% saline improves lung function; however, these concentrations are not always tolerable. Indeed, some subjects report using lower concentrations of saline to improve tolerability, but the effects of lower concentrations of NaCl are unknown. A recent randomised, blinded, placebo-controlled, parallel-group, multicentre study from Australia aimed to evaluate the relative effectiveness and tolerability of 0.9% *versus* 3% *versus* 6% saline nebulised twice daily with an eFlow rapid nebuliser. 3% saline significantly improved lung function and increased the time to first pulmonary exacerbation compared with 0.9% saline but did not improve quality of life. 6% saline had similar benefits to 3% saline but also significantly improved quality of life compared with 3% saline. Only 6% saline delayed the time to intravenous antibiotics for pulmonary exacerbation. Tolerability and adherence were similar. In conclusion dilution of 6% saline to 3% maintains the benefits for lung function and exacerbation prevention, but the positive impacts of 6% saline on quality of life and time to *i.v.* antibiotics for pulmonary exacerbations are lost (Dwyer TJ, 2023).

Low cost is a relevant property of HS.

Regarding issue 4

There is evidence to recommend the use of HS in CF but it should not be used in preference to rhDNAse. At this stage the benefit appears to be a reduction in pulmonary exacerbation frequency, though evidence does not exist to say it works in patients with frequent exacerbations. There are no data on the effects of HS in combination with rhDNase.

A recent review (Southern KW, 2019) explores the evidence supporting the use of dornase alfa, hypertonic saline, and mannitol in improving mucus clearance in patients with CF from different age groups with differing disease severity and the unanswered questions

regarding the optimal use of these agents.

A research question that also in the modulator era could be significant, in particular for people with severe lung disease and/or subjects not eligible to CFTR modulation, is:

Did people with CF and received dornase alpha and Hypertonic Saline (HS) have better preserved lung function than those treated with DA only?

Two studies evaluated this issue:

1) A registry study from US, involving patients followed between 2006 and 2014 (pre-CFTR modulators era) shows that subjects with $CF_{F508del}$ had no significant difference in lung function when nebulized HS was added to dornase for 1-5 years (Kaditis AG, 2023).

2) A registry study using UK CF Registry data from 2007 to 2018, emulated a target trial. The authors included people aged 6 years and over who were prescribed DNase without HS for 2 years. Moreover they investigated the effects of combinations of DNase and HS over 5 years of follow-up. Inverse-probability-of-treatment weighting was used to control confounding. The study concluded that for individuals with CF prescribed DNase, no evidence was found that adding HS had an effect on FEV_1% or prescription of intravenous antibiotics. (Granger E, 2023)

Regarding issue 5

A CDSR is available on this issue (Elkins M, 2020).

Some theoretical problems could afflict this issue: nebulisation of HS during physiotherapy could increase the complexity and the length of the overall session of airway clearance. Administration of HS after physiotherapy could reduce tolerability because of more direct interaction with the respiratory epithelium than with the mucus layer. Morning delivery may increase coughing during school or job whereas nocturnal administration could induce sleep disturbance.

The HS should also be inhaled after a short-term bronchodilator, because it has previously been established that this is necessary to prevent bronchoconstriction (Bye PTP, 2007).

While outcomes such as lung function did not show any difference between the regimens, people with cystic fibrosis perceived that inhaling hypertonic saline before or during airway clearance techniques may be more effective and satisfying than inhaling hypertonic saline after airway clearance. No studies comparing morning and evening inhalation were found.

In conclusion, timing of hypertonic saline inhalation makes little or no difference to lung function (low?certainty evidence). However, inhaling hypertonic saline before or during airway clearance techniques may maximise perceived efficacy and satisfaction. The long?term efficacy of hypertonic saline has only been established for twice?daily inhalations; however, if only one dose per day is tolerated, the time of day at which it is inhaled could be based on convenience or tolerability until evidence comparing these regimens is available.

The identified trials were all of very short intervention periods, so longer?term research could be conducted to establish the effects arising from regular use, which would incorporate the influence of changes in adherence with long?term use, as well as generating data on any adverse effects that occur with long?term use.

Regarding issue 6

A multicenter study compared the effect of NaCl 6.0% vs NaCl 0.9%. The patients were randomized to receive sinonasal vibrating inhalation of either NaCl 6.0% or NaCl 0.9% for 28 days, having a symptom score as primary outcome (Mainz JG, 2016). Sinonasal inhalation with NaCl 6.0% did not lead to superior results vs NaCl 0.9%.

Regarding issue 7

A recent study compared the aerosol characteristics of HS delivered by nebulizers of different operating principles (Breath-enhanced nebulizers [BEN] vs breath-actuated nebulizers [BAN] vs continuous-output nebulizers [CON]. The study showed that HS aerosols generated with the BEN and BAN devices were similar, while that generated with the CON was different. Airway delivery was similar between different brabds of BEN devices, but higher than that observed with the BAN and CON devices.

Regarding issue 8

The SIMPLIFY study aimed to assess the effects of discontinuing nebulised hypertonic saline or dornase alfa in individuals using the CFTR modulator elexacaftor plus tezacaftor plus ivacaftor (ETI). The SIMPLIFY study included two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials at 80 participating clinics across the USA in the Cystic Fibrosis Therapeutics Development Network. Individuals with cystic fibrosis aged 12-17 years with percent predicted FEV_1 ($ppFEV_1$) of 70% or more, or those aged 18 years or older with $ppFEV_1$ of 60% or more, if they had been taking ETI and either (or both) mucoactive therapies (?3% hypertonic saline or dornase alfa) for at least 90 days before screening were included. The main results was that in individuals with CF on ETI with relatively well preserved pulmonary function, discontinuing daily hypertonic saline or dornase alfa for 6 weeks did not result in clinically meaningful differences in pulmonary function when compared with continuing treatment (Mayer-Hamblett N, 2022).

Introduction of novel therapies for cystic fibrosis (CF), raises the question whether traditional treatments can be withdrawn. A research question is: In the pre-modulator era, did people with CF who were F508del homozygous ($CF_{F508del}$) and received dornase alpha and Hypertonic Saline (HS) have better preserved lung function than those treated with DA only? A recent registry study from US, involving patients followed between 2006 and 2014 (pre-CFTR modulators era) shows that subjects with $CF_{F508del}$ had no significant difference in lung function when nebulized HS was added to dornase for 1-5 years (Kaditis AG, 2023).

Unresolved questions

Long term clinical trials are needed to see the effect of HS in a sustained reduction in exacerbation frequency and to see if this translates to a more compelling improvement in quality of life.

Consideration should be given to a trial that assesses the effect of HS on individuals with frequent pulmonary exacerbations to see if this group has a greater response to treatment.

Consideration should be given to defining if there are patient groups that will respond better to HS or other mucociliary clearance agents, especially rhDNAse to better tailor the treatment.
Future trials should consider HS in conjunction with other mucociliary clearance regimes, or targeting individuals who fail to gain benefit from rhDNAse.

Trials that combine mucociliary agents also need to be considered to assess efficacy.

RCT comparing HS inhalation before versus after airway clearance physiotherapy should be conducted as much as it would be relevant to study whether HS should be inhaled in the morning versus in the evening.

A recent issue regards the fact that people with CF who are treated with the CFTR modulator ivacaftor are less likely to continue other treatments such as inhaled antibiotics, dornase alfa, hypertonic saline, chronic oral antibiotics and supplementary feeding, compared to people who are not treated with ivacaftor. In particular, the differences in use of dornase alfa and hypertonic saline solution between ivacaftor-treated and non-ivacaftor-treated people, are larger for people with higher lung function (Granger E, 2021). In order to evaluate changes in respiratory function for people with cystic fibrosis on triple combination therapy (Kaftrio™), the CF STORM trial will recruit pwCF age 12 years and above that have been established on Kaftrio™ therapy. They will have an equal chance of being allocated to either stop or continue their daily nebulised muco-active therapies (dornase alfa, hypertonic saline or both).
The trial is designed to provide confidence that stopping these nebulisers does not result in a significant decline in lung function over 12 months (https://www.cfstorm.org.uk/).

Keywords

Airway clearance drugs -expectorants- mucolytic- mucociliary-;