Mechanisms and applications of hypertonic saline

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DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
MRE

Contributorship
Both authors contributed equally

Acknowledgements
None

Introduction

Hypertonic saline is a strong sterile solution of salt water that can be inhaled as a nebulized medication for people with cystic fibrosis (CF). To examine how it should be applied clinically, it is worth considering the mechanisms by which it affects the disease process, and which signs, symptoms and other clinical outcomes it influences. Finally, it is worth considering how the effect is influenced by the dose received, and whether this should influence how it is applied in clinical practice. This paper will review this information and relate it to the clinical application of hypertonic saline.

Mechanisms of action

The taxonomy of mucoactive agents[1] consists of several classes of medications defined by their mode of action: mucolytics, expectorants, mucokinetics, ion-transport modifiers and other muco-regulatory compounds. It is difficult to classify hypertonic saline within this taxonomy because it has multiple mechanisms of action.

Mucolytics disrupt the structure of the mucus gel, thereby reducing its viscosity and elasticity. The intention of mucolytic therapy is therefore to make the viscoelasticity of the airway secretions better to facilitate their clearance from the airways. It has been suggested that hypertonic saline is not a mucolytic because mucolysis is not its primary mode of action.[2] However, hypertonic saline is capable of disrupting ionic bonds within the mucus gel, which could reduce cross-linking and entanglements.[3] This mucolytic effect may be why sputum markedly reduces its viscosity when hypertonic saline is added to it.[4] The thread-forming ability of CF sputum also reduces significantly with the addition of hypertonic saline.[5] These saline-mediated changes to the rheological properties of CF sputum are associated with improved transportability in a bovine tracheal model.[6,7] A similar mechanism – which does not directly affect the mucus gel itself – is that hypertonic saline dissociates DNA from the mucoprotein, which allows natural proteolytic enzymes to then digest the mucoprotein.[8] Therefore hypertonic saline appears to have several mucolytic mechanisms that do improve *in vitro* transportability of the mucus.

Another mucoactive class of medication is the expectorants, which add water to the airway surface. This is particularly relevant in the CF airway, because the abnormal or absent cystic fibrosis transmembrane conductance regulator (CFTR) protein does not initiate chloride ion secretion into the airway lumen and does not inhibit the absorption of sodium ions from the airway lumen via the epithelial sodium channel.[9] Because sodium ion absorption is increased and chloride ion secretion is decreased, insufficient salt is kept in the airway to maintain the usual hydration of the epithelial surface. This also results in dehydrated airway secretions and disruption to the mucociliary mechanism. This allows the retention of mucus, which becomes a nidus for infection.[10] *In vitro* measurements of the airway surface liquid on the epithelial surface show that hypertonic saline markedly increases the depth of this liquid layer – not just by depositing itself onto the surface, but also by osmotically drawing additional water onto the airway surface.[11] Depending on the dose of hypertonic saline achieved locally, the degree of restoration of the airway surface liquid varies, but it typically reaches a high peak transiently and returns close to its pre-treatment level within about 10 minutes, although it may have a

prolonged milder effect if the dose is adequate.[11,12] If excess water is drawn in to the airway, the mucus layer is able to accept it and to donate liquid back to the airway surface when required.[13] Thus excess water entering the airway osmotically is stored in the mucus layer, making its rheological properties more favourable for clearance.[4,5]

Another mucoactive class is the mucokinetics, which improve cough-mediated clearance by increasing airflow or reducing sputum adhesivity. We are unaware of any evidence that hypertonic saline has either of these immediate benefits, but it does trigger cough[14] and the cough increases the amount of mucus cleared from the lungs even further. The increase in mucociliary clearance with hypertonic saline and the extra clearance with cough have been objectively demonstrated *in vivo* in cystic fibrosis using radioaerosol studies.[15,16]

Hypertonic saline may also have some other mechanisms that are not strictly mucoactive. Recent *in vitro* research has shown that hypertonic saline reduces biofilm formation by *Pseudomonas aeruginosa* and the production of associated virulence factors.[17] Finally, hypertonic saline appears to increase the levels of two thiols that are protective against oxidative injury – glutathione and thiocyanate – in the airway surface liquid.[18]

Clinical benefits

An immediate benefit of the increase in mucus clearance is the opportunity to make a microbiological diagnosis in those patients who are unable to expectorate a sputum sample spontaneously. A single dose increases the chance of obtaining a sample in this population.[19–22] Of the 40 patients tested in these studies, 39 (97%) were able to produce a sample after inhaling various concentrations of saline up to 6%. Nineteen of these samples were tested for the presence of alveolar macrophages, and in 16 (84%) they were present.[19] For patients who can spontaneously expectorate, hypertonic saline significantly increases the size of their sample, whether measured by weight[21,22] or volume.[23] The colony counts and the percentage of non-squamous cells were also higher.[20,22] However, despite these better quality samples, the detection of pathogens did not improve, suggesting that hypertonic saline is not necessary when obtaining sputum samples for microbiological testing from patients with CF who can expectorate a sample spontaneously.

Riedler and colleagues[23] performed a cross-over trial in 10 adolescents with an exacerbation of their CF lung disease. Prior to a session of physiotherapy, subjects were randomized to inhale either 6% hypertonic saline or a normal saline control. On the following day, the alternate solution was inhaled prior to an identical physiotherapy session. Sputum was collected between the start of the inhalation and 60 min after the end of the physiotherapy regimen. Significantly more sputum was expectorated after hypertonic saline than control ($p = 0.006$). Subjects also rated how much clearer their chest felt after the physiotherapy, with significantly better scores when hypertonic saline had been used ($p = 0.04$) – an effect also reported in adults and children. Eng and colleagues[24] randomized 52 children and adults with CF to twice-daily inhalations of 6% hypertonic saline or a normal saline control. Within two weeks, the average FEV1 improvement among those taking hypertonic saline was 15% (SD 16), while the control group improved only 3% (SD 13) ($p = 0.004$). Two weeks after ceasing the inhalations, there was no significant difference in lung function.

A benefit in lung function appears to be maintained with long-term use. In a randomized trial in which 164 adults and children with CF participated, the hypertonic saline group maintained significantly higher lung function across the 48-week follow-up period.[25] Other clinical benefits were a reduction in the frequency and duration of exacerbations and fewer days missed from usual activities due to the disease. These benefits were accompanied by an improvement in several domains of quality of life. There was also close monitoring of sputum samples throughout the trial to check for any adverse effects on acquisition of organisms, organism density and inflammation. Overall, these outcomes showed no detrimental effect of long-term use of the twice-daily regimen of hypertonic saline inhalations. An often overlooked benefit was that patients in the active arm of the study rated their ease of clearing sputum as significantly greater at the end of the trial. This probably has important social implications. If patients can clear their secretions more effectively at the time of airway clearance, it

allows them to go about their work, study and social events with less concern about productive coughing during interactions with others.

No study has identified a subgroup of CF patients that responds particularly well to hypertonic saline therapy. For example, in the long-term trial, the effect of hypertonic saline on exacerbations did not differ significantly between users and non-users of physiotherapy, between subjects with mild or severe lung function impairment, nor between users and non-users of recombinant human deoxyribonuclease (rhDNase). We therefore recommend the therapy for most people with CF who find it tolerable.[26] Appropriate tolerability testing is described below.

Current research

An interesting feature of much of the research discussed above is the presence of dose-response relationships for hypertonic saline. The effects on viscosity and thread-forming ability increase as the concentration of saline increases.[4,5] The effect on the airway surface liquid also is much greater when a greater volume of hypertonic saline is applied to the epithelial surface.[11,12] The acceleration in mucociliary clearance also significantly increases as greater concentrations of saline are used.[15,16] However, side-effects such as cough also increase as the concentration increases. Therefore, some clinicians question whether patients who do not tolerate the standard dose would still benefit from a lower (but more tolerable) concentration of hypertonic saline. We have embarked on a randomized clinical trial (ACTRN12610000754044) that will compare the standard concentration of saline against a lower concentration of hypertonic saline, as well as against normal saline as a control condition.

Another approach to the issue of tolerability is to modify the hypertonic saline solution. Buonpensiero and colleagues[27] investigated hypertonic saline mixed with 0.1% hyaluronic acid – a naturally occurring polysaccharide. Hyaluronic acid appears to have several other mechanisms that may be beneficial in the CF airway, but Buonpensiero and colleagues examined its effects on tolerability and perceived saltiness of the combined solution compared to hypertonic saline alone. They noted improvements in the tolerability of hypertonic saline and reductions in the perceived salty taste when hyaluronic acid was included in the solution. These changes were both statistically and clinically significant.

The original long-term controlled trial of hypertonic saline only recruited participants as young as 6 years of age. The Infant Study of Inhaled Saline in Cystic Fibrosis (ISIS) will address this by examining the use of hypertonic saline in infants and children from 4 to 59 months (NCT00709280). The primary outcome of this trial will be the rate of protocol-defined pulmonary exacerbations requiring treatment with antibiotics, compared to the rate in the control group who will inhale normal saline.

While awaiting the outcome of these trials, we continue to recommend that hypertonic saline can be considered with most adults and older children with CF. If hypertonic saline therapy is being commenced with a patient, the first dose should be supervised, with spirometry and pulse oximetry before and after the dose to ensure that no clinically important airway narrowing occurs (i.e. a greater than 15% fall in FEV_1 or marked desaturation after a dose). All doses, including the initial test dose, should be preceded by a bronchodilator. Tolerability often improves over the first 10 doses, so patients who find the first doses difficult to tolerate should be encouraged to persevere, provided they are not showing signs of marked airway narrowing. Patients who do not pass their initial tolerability test can be re-tested at a later time; often the second test dose is tolerated much more readily.

Hypertonic saline is also being investigated as a treatment for non-CF bronchiectasis and chronic obstructive pulmonary disease (COPD). Although hydration of the airway surface may be less important than in CF, the other mechanisms of action of hypertonic saline all have the potential to work in bronchiectasis. The rationale behind the use in COPD is less clear, although clearance of retained secretions is accepted as a valid treatment target where they occur. Some studies have shown substantial overlap in pathology between COPD and bronchiectasis.[28,29] As hypertonic saline can cause airway narrowing, this should be very carefully monitored in trials of hypertonic saline in obstructive lung diseases such as COPD. Future trials will also assess the effect of hypertonic saline in combination with other classes of medications such as antibiotics or anti-inflammatory agents.

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