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Original Article

Hypertonic saline has a prolonged effect on mucociliary clearance in adults with cystic fibrosis

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Abstract

Background: Inhaled hypertonic saline (HS) has been shown to increase mucociliary clearance (MCC) and improve clinical outcomes in adults and adolescents with cystic fibrosis (CF). However, in younger children with CF, a large study failed to demonstrate clinical benefits. This discrepancy could reflect pharmacodynamic differences in the MCC response to HS in different populations. We previously demonstrated the absence of a sustained effect of HS on MCC in healthy adults and in this study sought to characterize the durability of the MCC response to HS in adults with CF.
Methods: At two study sites, MCC was measured in CF adults using gamma scintigraphy during three separate visits: at baseline, 15 min, and 4 h after a single dose of HS (7% NaCl, 4 mL). Particle clearance rates at these visits were used to assess the durability of the MCC response to HS.
Results: The average 90-minute clearance rate measured 4 h after HS was significantly increased (21.81% ± 12.8) when compared to baseline (13.77% ± 8.7, $p = .048$) and showed no apparent slowing relative to the rate measured 15 min after HS. While not all subjects responded to HS, the acute response strongly predicted the sustained effect in these subjects ($r = 0.896$, $p < .0001$).
Conclusions: These results suggest that, in contrast to healthy adults, a single dose of HS has a prolonged effect on MCC in adults with CF, which lasts at least 4 h. This may explain its clinical efficacy in this population.

Keywords: Hypertonic saline; Mucociliary clearance; Airway hydration; Pharmacokinetics

1. Introduction

Dehydration of airway secretions is believed to be a critical step in the pathogenesis of cystic fibrosis (CF) lung disease [1]. Impaired anion conductance through the cystic fibrosis transmembrane conductance regulator (CFTR) and accelerated sodium transport through the epithelial sodium channel (ENaC) cause dehydration of airway secretions, alter mucus rheological properties and impair mucus clearance [2–5]. Poor mucus clearance, in turn, promotes the development of chronic infection, inflammation, and progressive airways destruction [6]. Therapies such as hypertonic saline (HS) that increase the hydration of airway secretions are expected to improve mucociliary

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clearance (MCC) and, thereby, yield clinical benefits. Numerous studies have indeed demonstrated that HS acutely accelerates MCC in healthy and diseased individuals, including those with CF [7–10]. A year-long, placebo-controlled clinical trial of HS in CF patients by Elkins et al. demonstrated improved lung function, a marked reduction in exacerbation frequency and reduced requirement for antibiotic interventions [11]. As a result, approximately 70% of patients over 6 years of age currently use this therapy [12].

The efficacy of HS in older CF patients has also driven usage in younger populations. One third of patients under six years of age were prescribed HS in 2015 [12]. This practice has evolved despite a large, placebo controlled trial by Rosenfeld et al. that showed no improvement in clinical outcomes after one year of treatment in young CF children [13]. Interestingly, Laube et al. also found, on average, no significant improvement in MCC immediately after HS inhalation in young CF subjects (7–14 years) who had normal lung function [14]. Together, these data suggest that the physiologic response to treatment with HS may vary with the stage of disease and impact its resulting clinical efficacy.

Unfortunately, our understanding of HS effects on airway physiology is incomplete. In vitro studies using normal, human bronchial epithelial cultures suggested that HS has only a transient effect on airway surface liquid volume [7, 15]. Studies using CF epithelia yielded mixed results which depended upon the experimental conditions [7, 16, 17]. Previous in vivo measurements of MCC in adult CF subjects using gamma scintigraphy demonstrated that HS acutely accelerated clearance [7, 9, 10] and led to a sustained improvement (>8 h) in MCC after 2 weeks of repetitive treatment [7]. In contrast, in vivo measurement of MCC after HS in healthy individuals revealed that a single dose of HS only transiently increased mucus clearance, and in fact led to a significant, paradoxical slowing when measured 4 h post-dose [18]. These studies leave unanswered whether a single dose of HS may have a prolonged effect on MCC in adults with CF, in contrast to the data obtained in healthy individuals, or whether repeated doses are required to achieve a sustained improvement in MCC. A durable MCC response after a single dose of HS in adults with CF could explain the sustained effect seen with repetitive HS treatment, and might also provide a mechanistic framework to understand the differential clinical effects of HS in other disease populations, including young children with CF.

2. Methods

2.1. Study design & subjects

We conducted a two-center, randomized, open-label, cross-over study to measure the durability of the MCC response to a single dose of HS in individuals with CF at the University of North Carolina at Chapel Hill (UNC) and at Johns Hopkins University (JHU). Subjects were eligible for enrollment if they were ≥18 years of age and had confirmed, mild-to-moderate CF-related lung disease, defined by forced expiratory volume in one second (FEV_1) > 50% of predicted ($ppFEV_1$). Subjects were excluded if they were pregnant, had unstable disease as defined by an absolute decline in $ppFEV_1$ of >15% over the prior six months, demonstrated radiographic findings not considered part of the usual progression of CF-related lung disease, or had a change in symptoms or medical regimen in the preceding two weeks.

All subjects completed three separate MCC studies performed at baseline, 15 min after a dose of nebulized HS (7% NaCl, 4 mL, via PARI LC Star® nebulizer with PRONEB® Ultra Compressor), and 4 h after HS. Following enrollment, subjects underwent baseline MCC study and then were randomized to an order for which to complete the 15-minute and 4-hour studies. Each study was performed at least three but not >21 days apart. Prior to each study visit, subjects withheld HS and dornase alfa for at least 3 days. Long and short-acting bronchodilators were withheld before each study for 12 and 6 h, respectively. Subjects underwent spirometry testing following 2 puffs of albuterol from a metered dose inhaler on each study day prior to administration of HS (prior to MCC measurement on baseline study days), which served as a verification of the subject's clinical stability as well as pre-treatment prior to HS administration.

Informed consent was obtained from each subject prior to enrollment. The study was reviewed and approved by the institutional review boards at UNC and JHU. The study was registered on ClinicalTrials.gov (NCT01094704).

2.2. Measurement of MCC rate

During each study visit, subjects inhaled radiolabeled particles (Tc^{99m}-sulfur colloid) using a standard operating procedure at the two centers, followed by gamma scintigraphy, with only minor procedural variations [19]. In procedures performed at UNC, two fiducial markers containing Am^{241} (0.9 μCi each) were placed over the subject's spine at approximately C7 and L1 to facilitate alignment of the serial images obtained during the MCC scan, and a Co^{57} planar source was used to obtain a transmission image to define lung borders and regions of interest (ROI). At Johns Hopkins University, a low-dose external source of Tc99m was briefly held at the sternal notch of the patient before the start of each imaging procedure to assist with alignment of the subject with a reference mark on the computer screen. In place of a transmission scan, a Xe^{133} gas equilibrium scan, obtained by rebreathing 1–2 mCi of Xe^{133} through a Pulmonex system (Atomic Products, Shirley, NY) until equilibrium was achieved, was used to identify lung borders and define ROIs.

Radiolabeled sulfur colloid particles suspended in 0.9% saline were aerosolized with a jet nebulizer (DeVilbiss® Model 646; Mass Median Aerodynamic Diameter: 5 μm). In order to standardize particle deposition, subjects breathed in time to a metronome (1 beat/s) to maintain a 1-second inspiratory time, and used visual feedback to maintain an inspiratory flow rate of 0.5 L/s, as described previously [19]. Approximately 40 μCi was deposited in the lung over 2–3 min using real time monitoring. Immediately following isotope inhalation, subjects gargled and swallowed water to clear retained isotope from the oropharynx. Gamma emission images from the lungs were recorded serially over the ensuing 94 min using two-minute acquisitions. After an initial 64 min of imaging, subjects were asked to perform a series of 20 coughs every 10 min (60 coughs

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