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Inhaled Hypertonic Saline in Infants and Toddlers with Cystic Fibrosis: Short-Term Tolerability, Adherence and Safety

Margaret Rosenfeld, MD, MPH[1,*], **Stephanie Davis, MD**[2,*], **Lyndia Brumback, Ph.D.**[3], **Stephen Daniel, Ph.D.**[3], **Ron Rowbotham**[4], **Robin Johnson**[2], **Sharon McNamara, MN**[1], **Renee Jensen**[5], and **Felix Ratjen, MD, PhD, FRCP(C)**[5]

[1]Department of Pediatrics, University of Washington School of Medicine, and Seattle Children's Hospital, Seattle, WA

[2]Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, MD

[3]Collaborative Health Studies Coordinating Center and Department of Biostatistics, University of Washington, Seattle, WA

[4]Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, Seattle Children's Hospital, Seattle, WA

[5]Division of Pediatric Respiratory Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Canada

SUMMARY

Background—Inhaled hypertonic saline (HS) is an attractive agent for chronic maintenance therapy in infants and toddlers with cystic fibrosis (CF) because it improves defective mucociliary clearance. Prior to undertaking a clinical trial of HS efficacy in young children with CF, tolerability, adherence and safety must be established.

Methods—Three-center, open label evaluation of the short-term tolerability, adherence and safety of 7% HS administered twice daily for 14 days in children with CF 12 to 30 months of age. The primary objective was to evaluate the proportion of participants unable to tolerate single and repeated doses of 7% HS according to protocol-defined criteria. Participants inhaled a test dose of HS at the enrollment visit; test dose intolerance was defined as fulfillment of at least one of 4 criteria. Participants who tolerated the test dose inhaled 7% HS twice daily for 14 ± 2 days.

Results—20 children were enrolled. One was withdrawn due to maternal concern over fussiness with application of the facemask for the test dose. Of the 19 participants administered the test dose, 1 was withdrawn due to test dose intolerance (5%, 95% confidence interval 0, 26%). Eighteen participants completed the study; 1 was intolerant (95% CI 0, 27%) at the final visit due to new wheezes on exam in association with an upper respiratory infection and otitis media. Home symptom diaries demonstrated cough as the main symptom in the hour following inhalation, which decreased in frequency over the study period. Adherence as assessed by daily home diary and returned study drug ampoules was high. Participants reported receiving both treatments on a median of 100% of days; a median of 25 ampoules were used during a median of 13 days.

Conclusions—7% HS appears well tolerated for up to 14 days in infants and toddlers with CF, with high adherence. These results provide encouraging short-term tolerability and adherence data for future trials assessing the safety and efficacy of 7% HS in young children with CF.

Please send correspondence and requests for reprints to: Margaret Rosenfeld, MD, MPH, Division of Pulmonary Medicine, A5937, Seattle Children's Hospital, 4800 Sandpoint Way NE, Seattle, WA 98105, Phone (206) 987-5644, Fax: (206) 987-2639, margaret.rosenfeld@seattlechildrens.org.
*Drs. Rosenfeld, Davis, Brumback contributed equally to this article.

Keywords

safety; cystic fibrosis; infants; hypertonic saline

INTRODUCTION

Morbidity and mortality in patients with cystic fibrosis (CF) is predominantly due to progressive obstructive lung disease caused by chronic endobronchial infection and a vigorous host inflammatory response. Defective mucociliary clearance related to the underlying chloride channel abnormality predisposes patients with CF to this chronic airway infection [1,2]. It is now well established that CF lung disease begins in the first years of life, frequently prior to the onset of symptoms, providing a rationale for early intervention [3-10] Inhaled hypertonic saline (HS) is a particularly attractive agent to evaluate as a chronic maintenance therapy in infants and preschool children because it improves defective mucociliary clearance, an early step in the cascade of events leading to CF lung disease [11,12]. Prior to undertaking a clinical trial of the efficacy of HS in young children with CF, its tolerability, adherence and safety in this population must be established.

Three open-label [13-15] and two controlled studies [12,16] of 6% or 7% HS have been conducted in patients with CF older than 6 years of age. These studies demonstrated the tolerability and safety of HS in this age range, a beneficial effect on lung function, and a marked reduction in pulmonary exacerbations and missed days of work or school. The most commonly reported adverse effects were increased cough, chest tightness, throat irritation and a transient drop in FEV_1 immediately after HS administration. The rate of inability to tolerate HS due to cough ranged from 0 to 8%, and the rate of inability to tolerate HS due to any symptom ranged from 7 to 10%.

The only evaluations to date of the safety of HS in young children with CF are two single-dose studies [17,18]. Using the raised volume rapid thoracic compression technique, Subbarao, et al found no change in lung function associated with administration of a single dose of 7% HS to 13 sedated infants 25 to 140 weeks in age. Respiratory rate, heart rate and oxygen saturations also remained stable; 3 infants had cough during the inhalation. Dellon and colleagues administered a single dose of 3% HS to 14 infants and preschoolers with CF, and a single dose of 7% HS to 15 infants and preschoolers with CF. One preschooler had a >20% drop in FEV_1 after 7% HS; otherwise both doses were well-tolerated.

As no prior studies have evaluated the tolerability of and adherence to repeated doses of HS in young children with CF, we conducted a pilot three-center, open label evaluation of the short-term tolerability, adherence and safety of 7% HS administered twice daily for 14 days in children with CF 12 to 30 months of age. The primary objective was to evaluate the proportion of participants who were unable to tolerate single and repeated doses of HS according to protocol-defined criteria. We hypothesized that single and repeated doses of 7% HS would be well tolerated and safe in young children with CF.

MATERIALS AND METHODS

Participants, study visits and procedures

The study was performed at the pediatric CF centers of the University of North Carolina (UNC), Seattle Children's Hospital and Toronto Hospital for Sick Children. Children with a confirmed diagnosis of CF [19] 12 to 30 months of age were eligible to participate. Exclusion criteria included symptoms of an acute respiratory infection with onset in the preceding week, acute wheezing, oxygen saturation <95%, known intolerance of albuterol,

investigational drug use within the preceding 30 days, and current enrollment in a therapeutic clinical trial. The protocol was approved by the human subjects review board at each participating institution, and informed consent was obtained from the parents of all study participants.

At the enrollment visit, participants were administered albuterol, 2 puffs via metered dose inhaler with valved holding chamber attached to a face mask (Aerochamber, Monaghan Medical Corporation, Plattsburgh, NY). After a minimum of 5 minutes, 4 ml of 7% HS (Hyper Sal, PARI Respiratory Equipment, Inc., Midlothian, VA) was administered for 15 minutes via a PARI PRONEB® ULTRA compressor with a PARI LC® SPRINT Jr nebulizer equipped with a PARI BABY™ face mask. Administration of HS for 15 minutes with this nebulizer in a similar age range has been shown to result in nebulization of approximately half the dose (2.04 ± 0.2 ml)[18]. Participants were observed for intolerance for an additional 30 minutes. Oximetry, respiratory rate, auscultation of the chest and cough frequency were recorded at predefined intervals. Test dose intolerance was defined as fulfillment of one or more of four pre-defined criteria: a ≥10 breath per minute increase in respiratory rate for more than two minutes during quiet breathing, a ≥5% absolute drop in oxygen saturations for more than two minutes (e.g., from 98% to 93%), the presence of new wheezes or rales on exam, and sustained cough for more than 10 minutes or associated with post-tussive emesis. At the UNC site, sedated infant lung function was also performed at the enrollment visit before and after the test dose using the raised volume rapid thoracic compression technique and plethysmography [20,21], and the change in the forced expiratory volume in 0.5 seconds ($FEV_{0.5}$) was recorded. A drop of 20% in the $FEV_{0.5}$ value post-HS was defined as intolerance. Those who were intolerant of the test dose based on the pre-defined criteria were withdrawn.

Participants who tolerated the test dose were instructed to administer 2 puffs of albuterol followed in 5 to 30 minutes with 7% HS inhaled for 15 minutes twice daily at home for 14 ± 2 days, utilizing the same solution and device as used for test dose administration. For participants on multiple inhaled medications, the standardized order of inhalation was: albuterol, HS, dornase alfa, airway clearance, inhaled steroids, inhaled antibiotic. Families were instructed to complete a daily diary (see online supplement), electronically via a secure website or on paper, covering treatment adherence and symptoms. They were contacted by phone at Days 4 and 8, and returned for a follow-up visit after 14 ± 2 days. At the final study visit, study drug intolerance was defined as fulfillment of one or more of the following criteria: a ≥10 breath per minute increase in respiratory rate or a ≥5% drop in oxygen saturations compared to the enrollment visit (pre-HS); the presence of new wheezes or rales on exam; or a marked increase in cough, noisy or congested breathing, or emesis recorded in the daily symptom diary.

Sample Size and Statistical Analysis

For this descriptive pilot study, we planned to continue enrollment until 20 infants tolerated the HS test dose or until a maximum of 25 infants were enrolled, whichever occurred first. The sample size was based in part on the precision of the estimate of the proportion of participants intolerant to HS. Clinical characteristics among the study participants were described by means, standard deviations, and ranges, and by plots of measurements over time within participants. Adherence was evaluated by the number of returned treatment ampoules, by the number of reported treatment days, and by responses to diary adherence questions. Responses to daily diary questions were summarized by the proportion of participants with the response each day. In addition, the proportion of total days with the response was calculated for each participant, and the median of these proportions summarized.

RESULTS

Twenty two participants were screened and 20 were enrolled between October 2007 and April 2008 (7 at UNC, 6 at Seattle and 7 at Toronto). Infant lung function was measured before and after the HS test dose in 5 infants at UNC, and before the test dose only in 2 infants who awoke prematurely. Table 1 describes the baseline characteristics of the study participants.

At the enrollment visit, one participant was withdrawn after <1 minute of the test dose due to maternal concern regarding fussiness with facemask placement, so could not be evaluated for intolerance. Of the remaining 19 participants, 1 was intolerant of the test dose (5%, 95% confidence interval (CI) 0, 26%), based on a drop in oxygen saturation of >5% from baseline for more than 2 minutes (from 97% to 89%), and an increase of ≥10 breaths per minute in the respiratory rate compared to baseline for more than 2 minutes (from 29 to 41 breaths per minute). This patient also underwent infant lung function testing and had a 29% decline in $FEV_{0.5}$. She recovered after administration of 2 puffs of albuterol, and was withdrawn from the study. Eighteen subjects returned for the final study visit after a median of 14 days. At the final visit, one participant was intolerant (95% CI 0, 27%), due to new wheezes on physical exam. This participant had onset of signs and symptoms of an upper respiratory tract infection on Day 11, and was diagnosed and begun on antibiotics for an otitis media on Day 12.

The Figure shows respiratory rate and oxygen saturation versus time for the 19 participants who were evaluated for tolerance at the initial visit. It can be noted that one HS-tolerant participant had an 8% drop in oxygen saturation at the completion of the HS test dose, and one had an 11 breath per minute increase in respiratory rate 20 minutes after HS test dose completion. These changes were transient and therefore did not fulfill the criteria for HS intolerance.

The 18 participants who continued in the study after the first test dose completed a total of 232 daily diaries. The median number of diaries completed per participant was 13 (range 11-14). Separate diary questions evaluated increased symptoms in the hour after study drug inhalation and during each day *excluding* the hour after study drug inhalation. In terms of symptoms in the hour after a treatment, 39% (of 18 participants) reported more coughing on Day 1, falling to 8% (of 13 participants) on Day 13. The median percentage of days in which more coughing was reported in the hour after a treatment among the 18 participants was 18%. All other symptoms in the hour after treatment (more noisy or congested breathing, more rapid breathing, spitting up) were relatively rare (median 0%). In terms of daily symptoms excluding the hour after a treatment, more cough was reported in 11 to 50% of participants depending on the day (median 21%), and runny nose or sneezing was reported in 17 to 33% depending on the day (median 15%). All other symptoms (rapid breathing, noisy or congested breathing, spitting up) were relatively rare (median 0%).

From diary entries, the morning treatment was received by 75% to 100% of participants depending on the day. The median percentage of total days on which each participant received the morning treatment was 100%. Participants were instructed to inhale study drug for 15 minutes twice daily. The morning treatment lasted at least 10 minutes in 78% to 100% of participants who received the treatment depending on the day (median 100%). Results for the evening treatments were similar. Adherence estimated from the number of returned study drug ampoules was also high: a median of 25 study drug ampoules were used during a median of 13 days of treatment (each participant was expected to use 2 ampoules/day).

A total of 21 adverse events in 8 participants were reported (Table 2). These adverse events were reported to be “not serious” and to be of mild or moderate severity. One was reported to be “probably” related to treatment (increased cough within 1 hour of dose), 2 were reported to be “possibly” related to treatment (wheeze after dose without albuterol pre-treatment, chapped area around lips), and 18 were reported to be “unrelated” to treatment.

DISCUSSION

In this pilot study, inhaled 7% HS was well tolerated for up to two weeks in infants and toddlers with CF, with high treatment adherence. This study expands on the results of two prior single-dose safety studies of 7% HS in infants and preschool children with CF [17,18], as it is the first to assess acute tolerability in unsedated infants and to evaluate the safety of and adherence to repeated doses of HS in young children with CF. HS tolerability rates from our study as well as those of Subbarao, et al and Dellon, et al compare favorably with those reported in CF patients over 6 years of age. Of 19 participants evaluated for test dose intolerance, one was intolerant. Of 18 participants evaluated for intolerance at the final study visit one was intolerant. Based on home diaries, increased cough in the hour after study drug was observed in 39% of participants on Day 1, falling to 8% on Day 13. Runny nose or sneezing was reported in a median of 15% of participants across all study days, perhaps reflecting study recruitment from October through April. All other symptoms reported by parents were rare. Adherence, as reported by diaries and returned study drug ampoules, was also high, though this may not represent “real world” adherence rates due to the short duration of the study, close observation of the participants, and the selection bias of highly motivated families participating in research.

The safety of inhaled HS has also been evaluated in single and multiple-dose studies in young children without CF. Zar and colleagues administered a single dose of 5% HS to more than 600 children 1 month to 5 years of age with possible tuberculosis, HIV or suspected HIV, or intensive care unit admission due to pneumonia [22-24]. The most commonly reported side effects were wheezing that responded to bronchodilator therapy (< 2%) and cough (2% to 41%). Five studies have evaluated repeated daily doses of 3% HS as acute treatment for viral bronchiolitis in hospitalized or ambulatory non-CF infants [25-29]. In all five studies, a significant improvement in clinical symptoms was observed in patients treated with HS compared to patients receiving isotonic saline. No significant adverse events were ascribed to HS. Recently, high volume isotonic saline was found to be as effective as 3% saline in the treatment of mild bronchiolitis in infants evaluated in the emergency department. [28]. No adverse effects were ascribed to nebulized therapy among the 186 participants. Therefore, HS appears to be safe even in acutely ill infants with airway obstruction.

We chose to evaluate a concentration of 7% HS based on the results of a single-dose study of mucociliary clearance and tolerability of inhaled saline in concentrations ranging from 0.9% to 12% among 10 adults with CF [11]. Adverse event rates were not concentration-dependent in patients receiving 3% to 7% HS. However, 12% HS caused throat irritation in a higher percentage of patients compared to 3% or 7%, but did not further improve mucociliary clearance. Based on these findings, all subsequent studies of chronic administration of HS in CF patients have used a saline concentration of either 6% or 7% [12-16].

The dose of sodium chloride absorbed by inhalation of 7% HS should not place infants at risk of hypernatremia. Seven percent HS provides 1.2 mEq NaCl per mL of solution. After 15 minutes of nebulization of a 4 mL ampoule of HS in infants, about 2 mL of the original 4 mL has been nebulized [18]. If we assume that the entire nebulized dose is systemically

absorbed by the infant, then, with twice daily dosing, an infant would absorb 4.8 mEq of NaCl daily. CF infants are prescribed one-eighth teaspoon of table salt daily (as a supplement to avoid hyponatremic dehydration), which provides 12.5 mEq NaCl daily. In addition, the recommended daily allowance for sodium for healthy infants (not accounting for losses from the skin through sweating, which are increased in CF), range from 5.2 mEq per day for a 5 kg 6 month old to 13 mEq per day for a 16 kg toddler [30]. Thus, the additional sodium intake associated with inhalation of HS twice daily is small compared to both the recommended daily allowance of sodium and routinely prescribed table salt supplements, and should not pose a risk of hypernatremia.

The limitations of the current study must be highlighted. First, the sample size was small, limiting the precision with which we could estimate the rate of HS intolerance. Furthermore, 7 of the 20 participants received the test dose under sedation, which may alter the delivery and tolerability of inhaled drugs. On the other hand, sedation, required for infant lung function testing, did allow evaluation of physiologic response to acute inhalation of HS as measured by forced expiratory flows. In addition, the duration of exposure was relatively short (14 days), so that the safety of longer term exposure in this population remains unknown. Lastly, this study does not address the efficacy of inhaled HS in this population. Thus, it would be premature to introduce inhaled HS into clinical practice in children with CF <6 years of age based on the results of this pilot study.

In conclusion, results from this pilot study indicate that 7% HS is well tolerated and safe in infants and preschoolers with CF. Adherence is also high when 7% HS is administered twice a day for 14 days. We are currently conducting a randomized, double blind, controlled trial of the safety and efficacy of 7% vs. 0.9% HS inhaled twice daily for a year in children with CF <6 years of age. The results of this study will provide information regarding the efficacy and longer-term adherence and safety of HS in the youngest CF patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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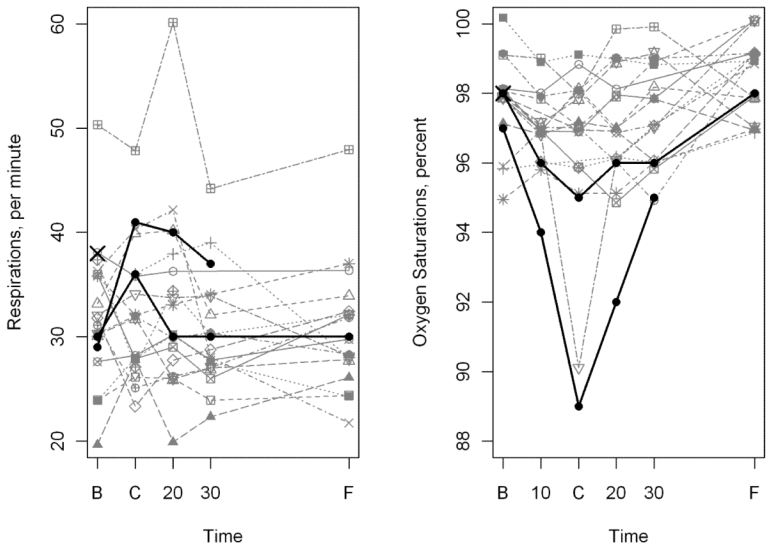

Figure 1.

Respiratory rate and oxygen saturation versus time in study participants. For time, B refers to baseline. Subsequent tick marks are at 10 minutes after baseline (oxygen saturations only), completion of the HS test dose, 20 and 30 minutes later, and the final study visit (day 14). Gray indicates subjects who were tolerant to the test dose. Black indicates subjects who were intolerant to test dose. X indicates subject who withdrew after <1 minute of test dose exposure.

Table 1

Baseline characteristics of enrolled subjects

	All (N=20)	Seattle (N=6)	UNC (N=7)	Toronto (N=7)
Age, months (mean (SD))	20.3 (5.2)	15.9 (3.6)	21.3 (5.1)	22.9 (4.5)
Gender, % male	35	50	14	43
Race, % Caucasian	90	100	100	71
Length, cm (mean (SD))	80.8 (5.3)	77.5 (3.3)	81.6 (5.2)	83 (6.0)
Weight, kg (mean (SD))	10.7 (1.8)	9.9 (0.9)	10.7 (1.9)	11.4 (2.1)
CF Genotype, % homozygous ΔF508	79*	80*	86	71
Respiratory rate	32 (6)	35 (3)	33 (3)	29 (10)
O2 saturation	98 (1)	97 (1)	97 (1)	98 (1)

* Genotype was not available for 1 subject from Seattle

Table 2

Reported Adverse Events

N	Adverse Event Description
Probably related to treatment	
1	increased cough within hour after dose
Possibly related to treatment	
1	wheezing after HS: did not pre-treat with albuterol
1	chapped area around lips
Unrelated to treatment *	
4	increased cough
3	rhinorrhea
2	otitis media
2	fever
2	emesis
1	chest congestion
1	eye infection
1	diarrhea
1	influenza
1	lethargy

* more than one adverse event may have occurred simultaneously in the same participant