A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis

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ABSTRACT

BACKGROUND
Inhaled hypertonic saline acutely increases mucociliary clearance and, in short-term trials, improves lung function in people with cystic fibrosis. We tested the safety and efficacy of inhaled hypertonic saline in a long-term trial.

METHODS
In this double-blind, parallel-group trial, 164 patients with stable cystic fibrosis who were at least six years old were randomly assigned to inhale 4 ml of either 7 percent hypertonic saline or 0.9 percent (control) saline twice daily for 48 weeks, with quinine sulfate (0.25 mg per milliliter) added to each solution to mask the taste. A bronchodilator was given before each dose, and other standard therapies were continued during the trial.

RESULTS
The primary outcome measure, the rate of change (slope) in lung function (reflected by the forced vital capacity [FVC], forced expiratory volume in one second [FEV₁], and forced expiratory flow at 25 to 75 percent of FVC [FEF₂₅₋₇₅]) during the 48 weeks of treatment, did not differ significantly between groups (P=0.79). However, the absolute difference in lung function between groups was significant (P=0.03) when averaged across all post-randomization visits in the 48-week treatment period. As compared with the control group, the hypertonic-saline group had significantly higher FVC (by 82 ml; 95 percent confidence interval, 12 to 153) and FEV₁ (by 68 ml; 95 percent confidence interval, 3 to 132) values, but similar FEF₂₅₋₇₅ values. The hypertonic-saline group also had significantly fewer pulmonary exacerbations (relative reduction, 56 percent; P=0.02) and a significantly higher percentage of patients without exacerbations (76 percent, as compared with 62 percent in the control group; P=0.03). Hypertonic saline was not associated with worsening bacterial infection or inflammation.

CONCLUSIONS
Hypertonic saline preceded by a bronchodilator is an inexpensive, safe, and effective additional therapy for patients with cystic fibrosis. (ClinicalTrials.gov number, NCT00271310.)
MUTATIONS IN THE CYSTIC FIBROSIS gene result in abnormal ion transport across the respiratory epithelium. In the absence of functional cystic fibrosis transmembrane conductance regulator protein, there is defective chloride secretion and excessive sodium absorption. Among the theories linking this genetic defect to lung disease in patients with cystic fibrosis is the isotonic volume-depletion hypothesis. It proposes that excessive absorption of salt from the airway lumen of patients with cystic fibrosis carries with it, dehydrating airway mucous secretions and depleting the volume of liquid on the airway surface. These changes disrupt the mucociliary mechanism, with retained mucus becoming the nidus for chronic infection. According to this hypothesis, the administration of hypertonic saline could be beneficial in patients with cystic fibrosis.

Experimental data suggest that a long-term clinical trial evaluating the safety and efficacy of hypertonic saline as a treatment for cystic fibrosis is warranted. For example, short-term administration of hypertonic saline is reported to improve the rheologic properties and transportability of sputum, hydration of the airway surface, and mucociliary clearance and lung function in patients with cystic fibrosis. Therefore, we designed a study to test the effect of long-term inhalation of hypertonic saline in patients with cystic fibrosis. The primary aim was to determine the effect of hypertonic saline on the linear rate of change in lung function. Secondary outcome measures included the level of lung function during treatment, the incidence of pulmonary exacerbations, antibiotic use, the number of days on which patients could not participate in their usual activities, results of quantitative microbiologic analyses, the quality of life, and the body-mass index (the weight in kilograms divided by the square of the height in meters).

METHODS

A parallel-group, randomized, controlled trial was conducted over a 48-week period. The ethics committee at each participating center approved the study. Each participant, or the legal guardian if the patient was younger than 18 years of age, provided written informed consent. The trial was designed and executed by the academic investigators. Pfizer Pharmaceuticals provided hypertonic saline and normal saline but otherwise did not participate in the design and conduct of the study; in the collection, analysis, or interpretation of the data; or in the writing or review of the manuscript.

SETTINGS AND PARTICIPANTS

Patients in clinically stable condition with a confirmed diagnosis of cystic fibrosis who were at least six years old were recruited from 16 adult or pediatric hospitals in Australia. Pregnant or breast-feeding women, persons colonized with Burkholderia cepacia, and cigarette smokers were excluded, as were those who had used hypertonic saline or non-routine antibiotics in the previous 14 days. The forced expiratory volume in one second (FEV$_1$), measured at screening, had to be within 10 percent of the best value obtained during the previous six months and at least 40 percent of the predicted value for height, age, and sex. The study was conducted between September 2000 and November 2003.

RANDOMIZATION

At a screening visit, demographic characteristics, spirometric values, and clinical data were recorded; sputum samples were collected; and patients filled out a questionnaire regarding their quality of life. Eligible participants returned for a baseline visit within seven days. In the interim, participants were assigned to a treatment group by means of a concealed, computer-generated randomization performed by a person not otherwise involved in the study. A minimization algorithm was used to balance the two groups with respect to age, FEV$_1$, presence or absence of long-term treatment with recombinant human deoxyribonuclease (rhDNase), use or nonuse of physiotherapy, and study center. Participants, their clinicians, the research assistants, and the trial coordinator remained unaware of the treatment assignments throughout the study.

INTERVENTIONS

Participants received 4-ml ampules of either 7 percent saline (the hypertonic-saline group) or 0.9 percent saline (the control group) (solutions were prepared by Pfizer); quinine sulfate (0.25 mg per milliliter) was added as a taste-masking agent. Solutions were nebulized with a Pari LC PLUS jet nebulizer and a Pari Proneb Turbo compressor.
bronchodilator was administered before each inhalation of the study solution. All other standard care was maintained throughout the trial.

At the baseline visit, spirometry and pulse oximetry were performed and participants then inhaled their usual bronchodilator or, for those who did not routinely use one, took two 100-μg puffs of albuterol (Ventolin) delivered by a metered-dose inhaler and Volumatic spacer (Allen & Hanburys). After 15 minutes, spirometry was repeated. Participants then inhaled the assigned study solution. Participants whose oxyhemoglobin saturation exceeded 90 percent and whose FEV₁ exceeded 85 percent of its prebronchodilator value after 15 to 30 minutes were eligible to proceed in the trial.

ASSESSMENT OF TRIAL OUTCOMES
Monitoring visits were scheduled at 4, 12, 24, and 36 weeks, and two visits were scheduled within 7 days of each other at 48 weeks. At each visit, participants filled out questionnaires regarding their quality of life, spirometry and a clinical assessment were performed, and sputum was collected. At all visits, a sputum sample was sent to the local laboratory for routine qualitative microbiologic analysis. A second sputum sample was collected at screening, baseline, and 4, 24, and 48 weeks and shipped on ice to a central laboratory for quantitative microbiologic analysis. Samples were handled according to protocols established for the North American Cystic Fibrosis Therapeutics Development Network Core Laboratory. Organisms were identified with the use of standard microbiologic techniques, including the API 20NE system (BioMerieux Vitek). Quantification of pathogens was performed with the use of the modifications of Wong et al.

Two definitions of a pulmonary exacerbation were used. The first was the clinical need for the intravenous administration of antibiotics, as indicated by the presence of 4 of 12 possible signs or symptoms: a change in sputum volume or color; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; a temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; a change in sinus discharge; a change in findings on physical examination of the chest; a decrease in pulmonary function by 10 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary infection. The second definition consisted of the presence of any 4 of the 12 signs and symptoms, regardless of whether any treatment was given. Participants completed a weekly diary card with detailed information regarding changes in symptoms and reported any unscheduled visits to a physician.

Antibiotic use was at the discretion of the attending physician in accordance with current practice, including the regular use of inhaled and oral antibiotics on an outpatient basis. There were no protocol-defined treatment or hospitalization rules for pulmonary exacerbations.

When a sufficient volume of sputum was available after quantitative microbiologic analysis, inflammatory and antiinflammatory cytokines were measured to assess the effect of hypertonic saline on airway inflammation. Sputum samples were liquified and homogenized according to the methods of Wolter et al. and then frozen for batch processing. Enzyme-linked immunosorbent assay kits were used with automated standard laboratory methods to measure interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor α (TNF-α).

The quality of life was measured with the use of a general health-related tool, the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36). The SF-36 consists of 36 items, 35 of which are aggregated to evaluate eight dimensions of health: physical function, pain, general and mental health, vitality, social function, and physical and emotional health. Scores on each subscale range from 0 to 10, and the summary scores range from 0 to 100, with higher scores indicating better health. The quality of life was also measured with the use of a questionnaire specific to cystic fibrosis: the Cystic Fibrosis Questionnaire for Adults and for Parents. Each instrument yields a score of 0 to 100, with higher numbers indicating better function for a number of quality-of-life domains related to health.

STATISTICAL ANALYSIS
Data were analyzed according to the intention-to-treat principle. The primary outcome measure — the linear rate of change in lung function from baseline — was assessed with the use of values obtained 0, 4, 12, 24, 36, and 48 weeks after randomization. The effect of the intervention was tested and estimated with the use of the time-by-treatment-group interaction term from
a mixed-effects model, which included age, sex, and height as covariates. Participants were treated as a random effect, and all other effects were fixed. As a secondary analysis, the absolute difference in lung function during the treatment period was compared between groups with the use of the treatment-effect term from the mixed-effects model including the same covariates plus baseline lung function. Values obtained before the administration of a bronchodilator were used for spirometric outcomes. P values of less than 0.05 were considered to indicate statistical significance. To reduce the risk of a type I error related to multiple comparisons, we used the multivariate mixed-effects model with the three measurements of lung function (FEV₁, forced vital capacity [FVC], and forced expiratory flow at 25 to 75 percent of FVC [FEF₂₅–₇₅]) included simultaneously as dependent variables and reported a single P value derived by this analysis. For the analysis of the linear rate of change in lung function, in which follow-up time was treated as a continuous variable, we assumed that the model had a compound-symmetry variance-covariance structure. For the analysis of the level of lung function, the variance-covariance structure was defined by the Kronecker product, which assumes an autoregressive correlation structure between follow-up visits and an unstructured correlation matrix across the three measurements of lung function.

Other secondary outcomes, including the quality of life, results of quantitative microbiologic analyses, and cytokine concentrations, were also assessed with the use of a mixed-effects model. Data across all measurement points, with adjustment for baseline values as a covariate, were used. The mean of the screening-day values and baseline values was used as the baseline.

The number of exacerbations and other events during treatment was compared between groups with the use of the Wilcoxon rank-sum test, and the interval in which participants remained free of exacerbations was compared with the use of Cox proportional-hazards regression. The number of events, such as hospitalizations or exacerbations, was adjusted for time spent in the study by multiplying the observed number of events by 336, which was the total number of days of study participation possible, divided by the number of days that the patient actually participated in the study. The rates of acquisitions of organisms in the hypertonic-saline and control groups were compared with the use of the chi-square test or, in cases in which subgroups were small, Fisher’s exact test. No adjustments for multiplicity were made across secondary outcomes, with nominal P values being reported. Interaction terms were used to conduct prespecified tests for differences in treatment-group effects according to age group, the FEV₁ at baseline, the use or nonuse of rhDNase, and the use or nonuse of physiotherapy.

We calculated that 164 participants would be required to give the study a statistical power of 80 percent to detect a change from baseline in FEV₁ equal to 10 percent of the predicted value between the hypertonic-saline and control groups at the 5 percent level. This estimation was based on published estimates of the standard deviation of the change in FEV₁ from baseline expressed as a percentage of the predicted value (19 percent) and the attrition rate (30 percent) in similar trials.

**RESULTS**

Between September 2000 and December 2002, 164 patients underwent randomization (Fig. 1). The baseline characteristics of the patients are shown in Table 1; domain scores reflecting the quality of life are shown in Table 4 of the Supplementary Appendix (available with the full text of this article at www.nejm.org).

After the administration of a bronchodilator for tolerance testing, both groups had a mean improvement in the FEV₁ of 60 ml. After the subsequent inhalation of the assigned solution, the FEV₁ fell by a mean of 94 ml in the hypertonic-saline group and 16 ml in the control group (see Fig. 5 in the Supplementary Appendix). Two participants had a decrease in their FEV₁ of more than 15 percent after the inhalation of hypertonic saline. However, on retesting, both subsequently passed the test and began taking the trial solution.

Inspection of the data showed that the FVC and FEV₁ appeared to increase during the first four weeks of treatment with hypertonic saline but remained essentially unchanged in the control group (Fig. 2). Thereafter, lung function plateaued in the hypertonic-saline group, and a difference in lung function favoring hypertonic saline persisted at all subsequent times. The test
LONG-TERM HYPERTONIC SALINE IN PATIENTS WITH CYSTIC FIBROSIS

Figure 1. Enrollment and Outcome.
of the linear slope of lung function, incorporating FEV₁, FVC, and FEF₂₅₋₇₅ into a single model, through all times from 0 weeks (baseline) to 48 weeks revealed no significant difference between the two groups (P = 0.79) (Table 2). However, the absolute level of lung function, averaged over the period from 4 weeks to 48 weeks after randomization, was higher in the hypertonic-saline group than the control group (P = 0.03) (Table 2). Expressing the absolute differences in lung function during this period as a percentage of individual baseline values, the FEV₁ was 3.2 percentage points (95 percent confidence interval, 0.1 to 6.2 percentage points) higher in the hypertonic-saline group than the control group and the FVC was 2.8 percentage points (95 percent confidence interval, 0.4 to 5.2 percentage points) higher in the hypertonic-saline group.

The effect of treatment on the linear rate of change in lung function did not differ significantly according to the baseline FEV₁, the use or nonuse of rhDNase, age group, or the use or nonuse of physiotherapy. The effect of treatment on the absolute level of the FVC and FEV₁ during the
post-randomization period did not differ significantly according to the baseline FEV₁, the use or nonuse of rhDNase, or the use or nonuse of physiotherapy. The effect of treatment on the absolute level of FVC, but not of FEV₁, did differ significantly between adults and children (P=0.01). For participants who were at least 18 years of age, the absolute level of FVC during the treatment period was 175 ml higher (95 percent confidence interval, 56 to 294; P=0.004) in the hypertonic-saline group than in the control group, whereas among participants who were younger than 18 years of age, the FVC did not differ significantly between groups (1 ml higher in the control group; 95 percent confidence interval, −72 to 70; P=0.98).

There were fewer exacerbations requiring intravenous antibiotic therapy in the hypertonic-saline group than in the control group. The mean number of exacerbations per participant in the control group was 0.89, as compared with 0.39 in the hypertonic-saline group (difference, 0.5; 95 percent confidence interval, 0.14 to 0.86; P=0.02). The mean number of days on which participants met this exacerbation definition was 17 days in the control group and 6 days in the hypertonic-saline group (difference, 11 days; 95 percent confidence interval, 3 to 19; P=0.02). The interval during which participants remained free of exacerbations was significantly longer in the hypertonic-saline group than in the control group (P=0.03), with a 48-week exacerbation-free survival rate of 76 percent in the hypertonic-saline group and 62 percent in the control group (Fig. 3A).

When exacerbations were defined according to signs and symptoms alone, regardless of treatment, results again favored the hypertonic-saline group. The mean number of exacerbations defined in this way was 2.74 per participant in the control group and 1.32 in the hypertonic-saline group (difference, 1.42; 95 percent confidence interval, 0.86 to 1.99; P<0.001). The mean number of days during which participants met criteria for a symptom-defined exacerbation was 69 days in the control group and 22 days in the hypertonic-saline group (difference, 47 days; 95 percent confidence interval, 30 to 63; P<0.001). The time participants remained free of exacerbations was significantly longer in the hypertonic-saline group (P<0.001), with a 48-week exacerbation-free survival rate of 41 percent in the hypertonic-saline group and 16 percent in the control group (Fig. 3B). The effects of hypertonic saline on exacerbations did not differ significantly between participants who used rhDNase and those who did not use rhDNase.

As an index of total antibiotic use for symptom-defined exacerbations, the number of “antibiotic-days for exacerbations” was calculated by summing the number of days spent taking each antibiotic prescribed for an exacerbation, regardless of any overlap of different antibiotics. The median number of antibiotic-days for exacerbations was 50 (interquartile range, 6 to 144) in the control group, whereas it was significantly
lower, at 11 (interquartile range, 0 to 49) in the hypertonic-saline group (P<0.001). The two groups did not differ significantly in the number of antibiotic-days for any reason (median number in the control group, 167; interquartile range, 56 to 388; and median number in the hypertonic-saline group, 144; interquartile range, 36 to 351; P=0.29) or in the number of intravenous-antibiotic-days for any reason (0 in the control group; interquartile range, 0 to 34; and 0 in the hypertonic-saline group; interquartile range, 0 to 25; P=0.46).

Participants in the hypertonic-saline group had significantly fewer days on which they were absent from school or work or unable to participate in other, usual activities: 7 days (interquartile range, 0 to 21), as compared with 24 (interquartile range, 12 to 48) in the control group (P<0.001). Participants in the hypertonic-saline group had significantly fewer days on which they were absent from school or work or unable to participate in other, usual activities: 7 days (interquartile range, 0 to 21), as compared with 24 (interquartile range, 12 to 48) in the control group (P<0.001). There was no significant difference in weight or body-mass index between the groups. The number of hospitalizations and unscheduled visits to the hospital also did not differ significantly between the groups.

The mental health domain of the SF-36 was a mean of 5.2 points higher in the hypertonic-saline group than the control group (P=0.02). For participants who were at least 14 years old, there were significant differences between groups in favor of hypertonic saline in the role domain (7.3 points, P=0.04), the emotional domain (4.8 points, P=0.03), and the health domain (5.3 points, P=0.01) of the Cystic Fibrosis Questionnaire for Adults. For participants who were younger than 14 years of age, the digestion domain of the Cystic Fibrosis Questionnaire for Parents was a mean of 6.4 points higher (better) in the control group than in the hypertonic-saline group (P=0.02).

The difference between groups in all other domains was not significant.

Overall, hypertonic saline did not significantly alter the concentration of *Pseudomonas aeruginosa* in sputum (Fig. 4A). Among participants who were younger than 18 years of age, the concentration of *P. aeruginosa* in sputum was lower in the control group than in the hypertonic-saline group (P=0.04), reflecting a single, unsustained drop in values in the control group at four weeks (Fig. 4B). Hypertonic saline did not significantly alter the concentration of *Staphylococcus aureus* in sputum (Fig. 4C). The prevalence of *P. aeruginosa* and *S. aureus* did not differ significantly between groups. The incidence of acquisition of *P. aeruginosa*, *S. aureus*, *B. cepacia*, *Stenotrophomonas maltophilia*, *Candida albicans*, aspergillus species, and *Haemophilus influenzae* did not differ significantly between groups. There were five new acquisitions of coliform bacteria in the control group and none in the hypertonic-saline group (P=0.03).

There was no significant difference between groups in the concentration of interleukin-6 (P=0.94), interleukin-8 (P=0.36), interleukin-10 (P=0.81), or TNF-α (P=0.38) across the post-randomization measurements, after adjustment for baseline values.

Adverse events included respiratory exacerbations, chest pain, gastrointestinal symptoms, headache, joint pains, pharyngitis, and tonsillitis. There were significantly fewer adverse events in the hypertonic-saline group than the control group (mean, 2.89 vs. 5.17 per 336 days; P<0.001). Adverse drug reactions (i.e., adverse events that in the opinion of the examining investigator were directly and temporally related to the inha-

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### Table 2. Effect of Hypertonic Saline on Lung Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Difference in Linear Rate of Change of Lung Function from 0–48 Wk</th>
<th>Absolute Difference in Lung Function Across Wk 4 to 48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/wk (95% CI)</td>
<td>ml (95% CI)</td>
</tr>
<tr>
<td>FEV₁</td>
<td>0.3 (−1.3 to 1.8)</td>
<td>68 (3 to 132)</td>
</tr>
<tr>
<td>FVC</td>
<td>0.5 (−1.3 to 2.3)</td>
<td>82 (12 to 153)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅</td>
<td>−1.5 (−4.2 to 1.2)</td>
<td>39 (−67 to 146)</td>
</tr>
</tbody>
</table>

* The differences shown are those between the hypertonic-saline and control groups. Positive values represent a benefit from hypertonic saline. Values were adjusted for age, height, and sex. CI denotes confidence interval, FEV, forced expiratory volume in one second, FVC forced vital capacity, and FEF₂₅₋₇₅ forced expiratory flow at 25 to 75 percent of the forced vital capacity.

† Four weeks is the first post-baseline measurement. The analysis was adjusted for baseline values.
lation of the trial solution) were significantly more common in the hypertonic-saline group (P=0.001) (Table 3). Six of these resolved when the participants elected to stop taking the trial solution permanently. The remainder resolved after a mean of 15 days, with no interruption of the treatment regimen, temporary cessation of treatment, or reduction of the dosing frequency.

Compliance with treatment, as judged by the number of returned ampules, was 63 percent in the control group and 64 percent in the hypertonic-saline group. Quarterly data are presented in Table 5 of the Supplementary Appendix. Only 38 percent of participants (49 percent of the hypertonic-saline group and 27 percent of the control group) were able to guess their treatment assignment correctly. Most attributed their choice to the perceived therapeutic effect.

**DISCUSSION**

In this long-term trial, we compared the safety and efficacy of hypertonic saline with those of isotonic saline in patients with cystic fibrosis. Treatment with hypertonic saline for approximately one year had no significant effect on the rate of change in lung function, but it was associated with a moderate yet sustained improvement in the level of lung function. More dramatic, however, were the reductions in the number of exacerbations, antibiotic use for exacerbations, and absenteeism from school or work or the inability to engage in other, usual activities that were associated with the use of hypertonic saline.

This apparent divergence between small improvements in lung function and large reductions in the frequency of exacerbations has been observed in other studies of patients with cystic fibrosis. A possible mechanism for this dichotomy is presented in an article by Donaldson and colleagues in this issue of the *Journal.*

A decrease in exacerbations is an important outcome for patients with cystic fibrosis with respect to the quality of life, days absent from normal activities, and cost. Furthermore, exacerbations associated with infections typically worsen the progression of lung disease in these patients. Accordingly, the frequency of exacerbations is a strong predictor of morbidity and mortality. Thus, a treatment that reduces exacerbations is of major clinical relevance. Because hypertonic saline achieves this outcome at a low cost relative to that of other proven therapies for cystic fibrosis, it is an attractive addition to the therapeutic armamentarium. Furthermore, treatment with hypertonic saline reduced indirect costs to patients and the community by reducing absenteeism.

The beneficial effects of hypertonic saline could be due to increased clearance of mucus as a result of increased hydration of the airway.
Donaldson et al. report evidence in support of the first mechanism. Specifically, they showed that hypertonic saline promoted sustained increases in mucociliary clearance in patients with cystic fibrosis and provided in vitro data describing a possible mechanism — namely, slow diffusion of hypertonic saline from airway surfaces from such patients.

Given the hypothesis that hypertonic saline could inactivate endogenous antimicrobial compounds in patients with cystic fibrosis,28,29 our finding that there was no convincing evidence of enhanced bacterial growth with hypertonic saline was reassuring. The significant difference between groups in the concentration of P. aeruginosa in sputum in the subgroup of patients who were younger than 18 years of age was due primarily to a single data point representing an unexplained and unsustained drop in the concentration in the control group at four weeks. This drop did not appear to indicate a clinically important detrimental effect of hypertonic saline. The absence of an increase in the rate of acquisition of common organisms in the hypertonic-saline group also provides reassurance. Furthermore, the analysis of sputum cytokines, including interleukin-8, which is considered to be a key marker of inflammation in patients with cystic fibrosis,30,31 revealed no evidence that hypertonic saline induced airway inflammation.

Adverse events, which often reflect the effects of the disease in patients with cystic fibrosis, were less common in the hypertonic-saline group, a finding consistent with the efficacy described above. Immediate adverse reactions to the administration of hypertonic saline resolved rapidly in the few patients who had them. Cough can be expected with the introduction of this therapy, but in our experience, it typically decreases over time. We should also stress the fact that to prevent or minimize airway narrowing, a bronchodilator must be given before the administration of hypertonic saline.

In conclusion, our results provide proof of...
principle that adding salt (and water) to the airway surfaces of patients with cystic fibrosis is beneficial. Long-term treatment with hypertonic saline improved lung function, reduced the frequency of exacerbations, and reduced absenteeism in both children and adults. Hypertonic saline was associated with few treatment-related adverse events and improved important domains related to the quality of life, and its benefits were independent of treatment with rhDNase. Hypertonic saline preceded by a bronchodilator is an inexpensive, safe, additional therapy in patients with cystic fibrosis.

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No potential conflict of interest relevant to this article was reported.

We are indebted to the patients and parents who volunteered to participate in the study; to Pfizer Australia for manufacturing the saline solutions; to Puri Germany and Techniporo Australia for supplying the compressors and nebulizers; to Allen & Hanburys, a Division of Glaxo Wellcome Australia, for supplying albuterol metered-dose inhalers and spacers; to Prof. Richard Boucher and Dr. Scott Donaldson for their careful review of this article; to Dr. Lisa LaVange for her advice regarding the statistical analysis; and to Profs. Malcolm King and Warrick Britton for their helpful advice.

Table 3. Adverse Reactions Considered to Be Related to Treatment.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Control</th>
<th>Hypertonic Saline</th>
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</thead>
<tbody>
<tr>
<td>Cough</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Chest tightness</td>
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<tr>
<td>Pharyngitis</td>
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<td><strong>Total</strong></td>
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*P = 0.01.


REFERENCES


