Pulmonary

Airway-Rehydrating Agents for the Treatment of Cystic Fibrosis: Past, Present, and Future

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OBJECTIVE: To review and evaluate airway-rehydrating agents used for the treatment of cystic fibrosis (CF).

DATA SOURCES: Literature was retrieved through MEDLINE (1977-August 2010), Cochrane Library, and *International Pharmaceutical Abstracts* (1977-August 2010). Search terms used included hypertonic saline, inhaled mannitol, denufosol, Moli1901, lancovutide, and cystic fibrosis. Reference citations from selected articles were reviewed.

STUDY SELECTION AND DATA EXTRACTION: All articles published in English identified from the data sources were evaluated for inclusion. Clinical trials in humans and relevant review articles were evaluated for each airway-rehydrating agent.

DATA SYNTHESIS: Use of airway-rehydrating agents for the treatment of CF is an expanding area. Hypertonic saline (7% NaCl) is currently the only commercially available airway-rehydrating agent recommended for chronic therapy in patients with CF and is being evaluated in younger patients. Inhaled mannitol is an investigational dry-powder inhalation agent that improves mucus clearance in a similar manner to hypertonic saline and produced a statistically significant increase in forced expiratory volume in 1 second in a Phase 3 trial. Denufosol, a $P2Y_2$ agonist, rehydrates the airway surface liquid bypassing the basic CF transmembrane conductance regulator (CFTR) protein defect. It produces improvement in pulmonary function and is being further evaluated in a Phase 3 trial. Lancovutide (Moli1901) is an investigational agent in early-phase trials that activates a calcium-dependent chloride channel, allowing chloride to enter the airway.

CONCLUSIONS: Hypertonic saline is the primary airway-rehydrating agent used in the treatment of CF. Inhaled mannitol may become an alternative to hypertonic saline since it is faster and easier to administer. It remains unclear whether denufosol and lancovutide will be synergistic or antagonistic with hypertonic saline. Both agents have a unique mechanism of action that bypasses the basic CFTR defect.

KEY WORDS: cystic fibrosis, denufosol, hypertonic saline, inhaled mannitol, lancovutide, Moli1901.

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Cystic fibrosis (CF) is a lethal genetic disease that is most common in the white population. It is an autosomal recessive genetic disease that is caused by a mutation in a gene on chromosome 7 that encodes for the CF transmembrane conductance regulator (CFTR) protein. Over 1500 CFTR mutations have been identified,[1] the most common of which is delta F508. The average life expectancy for a patient with CF is 37 years.[1]

CF causes numerous exocrine organ manifestations including pulmonary disease, gastrointestinal abnormalities, hepatic and pancreatic disease, and reproductive dysfunction. Due to the complexity of the disease, patients typically require numerous long-term medications. Research is ongoing to find new treatments to help slow the disease progression and cure CF. Drugs in development with novel mechanisms of action present new approaches to treatment. These agents have been or will be added to already complex medication regimens and it is important for pharmacists and other health-care professionals to become familiar with these emerging treatment options.

Cystic Fibrosis Lung Disease

Pulmonary disease is only one of the manifestations of CF; however, it accounts for 85% of CF-related deaths.[2] When CFTR is absent or its function is reduced, chloride cannot be secreted into the airway surface liquid (ASL) (Figure 1). This disrupts the equilibrium between chloride, sodium, and water that is normally present in the ASL, causing sodium to be pulled from the ASL, with water following. The dehydrated ASL becomes thick

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and viscous, making it difficult for ciliary function to clear it from the airways. The viscous ASL creates an ideal environment for trapped bacteria, which can lead to colonization and/or infection. Pulmonary bacterial colonization also promotes chronic inflammation, and the resultant cycle of infection and inflammation leads to lung damage and progressive loss of pulmonary function.[1]

Various strategies to reduce mucus plugging and increase mucociliary clearance are employed in CF treatment. Physical airway clearance, also known as chest physiotherapy, is the mainstay of airway clearance therapy. Clearance methods include percussion and postural drainage, autogenic drainage, and high-frequency chest wall or airway oscillation devices such as Thera-Vest and Acapella.[3] These airway clearance methods have been approved by the Cystic Fibrosis Foundation and selection is based on individual patient characteristics and performance.[4] Airway clearance therapies such as these are used as maintenance treatment to facilitate the expectoration of mucus from the lungs. Therapeutic bronchoscopy with lavage has also been used to help remove mucus obstruction from the airways and to allow culture and sensitivity testing.[5]

Pharmacologic interventions to improve mucus clearance include *N*-acetylcysteine (NAC) and dornase alfa. NAC facilitates mucus clearance by breaking disulfide bonds in the mucus; however, NAC is unpleasant for the patient due to smell and airway irritation if administered via the inhaled route. NAC can also be administered orally with similar effects as when it is inhaled. There is little evidence to support the use of NAC in CF[2] and with the advent of more tolerable agents it is not frequently prescribed. Inhaled amiloride, a sodium channel blocker, was studied in CF to inhibit sodium transport in the lung via the epithelial sodium channel. Despite researchers' early optimism, clinical trials failed to show a beneficial effect, potentially due to amiloride's short half-life.[6] The mechanism of action of dornase alfa is to cleave extracellular DNA from expended neutrophils and other inflammatory cells in the CF mucus, thus reducing viscosity and promoting clearance. CF treatment guidelines recommend the daily use of dornase alfa in patients with CF older than 6 years.[2]

Antiinflammatory agents are used for maintenance treatment in CF to reduce inflammation in the lungs and reduce lung damage and include azithromycin 3 times per week and high-dose ibuprofen. During acute CF exacerbations, intravenous and oral antibiotics are used to reduce bacterial colonization. Inhaled antibiotics may also be used in acute exacerbations or as chronic suppressive therapy. Inhaled antibiotics that are commonly used include tobramycin and colistin. Inhaled aztreonam is newly approved for use in CF.

Another strategy to alter the airway environment of the CF lung and potentially decrease bacterial colonization is to increase the volume of the ASL. A variety of strategies have been employed to augment the ASL, including use of osmotic agents that pull water into the ASL, chloride secretion through the activation of non-CFTR–dependent pathways, and inhibition of sodium absorption. Increasing the volume of the ASL helps decrease viscosity, improves clearance, and reduces pulmonary exacerbations and can be accomplished by administration of an airway-rehydrating agent such as hypertonic saline (7% NaCl). Hypertonic saline is currently the only commercially available airway-rehydrating agent, although several others are being investigated for use in CF. The most promising of these newer agents include inhaled mannitol (Pharmaxis), denufosol (Inspire Pharmaceuticals), and lancovutide (Lantibio Inc.). Two other airway-rehydrating agents in early-phase studies, GS9411 (Gilead Science Inc.), an inhaled epithelial sodium channel antagonist,[7] and cobiprostone (SPI-8811) (Sucampo Pharmaceuticals, Inc.), an oral agent that bypasses defective chloride channels,[8] are promising drugs but are not reviewed here due to lack of published clinically focused literature at the time of writing. This article reviews literature evaluating the use of airway-rehydrating agents in CF. Relevant articles were identified through MEDLINE (1977-August 2010), Cochrane Library, and *International Pharmaceutical Abstracts* (1977-August 2010). Search terms included hypertonic saline, inhaled mannitol, denufosol, lancovutide (Moli1901), and cystic fibrosis. Search results were reviewed for relevance and selected article references were also reviewed. Articles included were primary studies and when appropriate, review articles addressing primary evaluative studies.

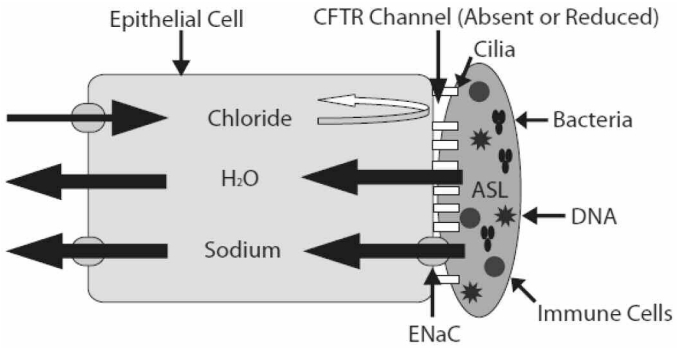

Figure 1. Schematic of water and sodium chloride transport in the epithelial cell of the cystic fibrosis airway. ASL = airway surface liquid; CFTR = cystic fibrosis transmembrane conductance regulator; ENaC = epithelial sodium channel.

Hypertonic Saline

Hypertonic saline is administered by nebulization in patients with CF to increase the hydration of the ASL. The therapeutic applica-

tion of hypertonic saline originated in Australia when pulmonologists noticed that patients with CF who surfed had generally improved lung function as compared to other patients with CF.[9] The exact mechanism of action of hypertonic saline remains unclear, but the most commonly accepted theory is that it acts osmotically to pull water into the airways to hydrate the mucus.[10,11] Some other proposed mechanisms of action include breaking ionic bonds in the mucus, thus reducing repulsion of negative charges in the mucus, allowing the mucus to become more compact.[12] Hypertonic saline is also proposed to decrease the motility of *Pseudomonas aeruginosa*.[13]

Hypertonic saline is commercially available as 7% unit dose 4-mL vials. The selection of the 7% concentration was based on a dose-ranging study comparing mucus clearance following nebulization of 0.9%, 3%, 7%, and 12% NaCl. Clearance increased with increasing concentrations; however, patients in the 12% group experienced throat irritation and other adverse effects. It was determined that 7% NaCl provided the best mucus clearance with the most acceptable degree of adverse effects (Table 1).[14]

The short-term efficacy of hypertonic saline was established in a clinical trial comparing 0.9% NaCl and 6% NaCl administered twice daily for 2 weeks. This study demonstrated an improvement in forced expiratory volume in 1 second (FEV_1) during the treatment period, which diminished following discontinuation (Table 1).[15] Another 2-week study compared 7% NaCl 4 times a day with or without amiloride pretreatment. Amiloride, a sodium-channel blocker, was hypothesized to extend the duration of action of hypertonic saline. NaCl 7% without amiloride pretreatment had improved mucus clearance and pulmonary function, but NaCl 7% with amiloride did not (Table 1).[16] In a longer study, the degree of change in pulmonary function over a 48-week treatment period was not significantly ($p = 0.79$) different between the hypertonic saline group and the placebo group; however, the average absolute pulmonary function measurements were higher in the hypertonic saline group. Although the pulmonary function improvement was not numerically large, there was a 56% decrease in the exacerbation rate in the hypertonic saline group (Table 1).[17]

The current guidelines for the use of nebulized 7% NaCl in CF endorse long-term, twice-daily therapy for patients older than 6 years.[2] It may be prudent to administer bronchodilator therapy prior to nebulized hypertonic saline to decrease the incidence of bronchospasm and to improve mucus clearance.[10] Cough is a common adverse effect when inhaled hypertonic saline is initiated, but usually resolves with continuation of therapy. Some patients cannot tolerate the 7% NaCl formulation, even with bronchodilator pretreatment. For these patients an NaCl solution of 5%, 4%, or 3% can be used. The 4% NaCl formulation requires careful dilution from concentrated NaCl solution (14.6% or 23.4%). The 3% and 5% strengths are available as intravenous formulations, which can be used directly for inhalation.

Studies on the safety and tolerability of hypertonic saline in children aged 4 months to 7 years demonstrated that both 3% and 7% NaCl formulations were well tolerated in this age group (Table 1).[18] The long-term efficacy of hypertonic saline in children younger than 6 years is currently being evaluated. At the time of this review, the ISIS (Infant Study of Inhaled Saline) trial was still recruiting patients.[19] The results of this study will help determine whether early initiation of hypertonic saline therapy may improve long-term outcomes for infants with CF.

Hypertonic saline therapy is generally initiated with a 4-mL dose of the 7% solution nebulized twice daily using the PARI LC Plus nebulizer and PariPARI Proneb Turbo compressor. One of these doses takes approximately 15 minutes to administer. The Cystic Fibrosis Services Pharmacy reports the current cost for a 30-day supply of this dose is $59.50.[20] The eventual cost-benefit analysis of newer airway-rehydrating agents will be very important to assess the best option for the patient.

Inhaled Mannitol

Inhaled mannitol is an investigational airway-rehydrating agent that has been used in patients with asthma for bronchial provocation testing[21] and for improving mucus clearance in patients with bronchiectasis.[22] The mechanism of action is similar to that of hypertonic saline as an osmotic agent to draw water into the ASL.[23] Mannitol is a sugar and there is concern that inhaling mannitol into the airways may increase the biofuel available for colonized bacteria such as *P. aeruginosa*.[24] The impact of increasing the fuel source in the CF lung is unclear; however, clinical trials with inhaled mannitol have not demonstrated harmful changes in the microbiologic (bacterial and fungal) content of subjects' sputum.[23,25] Inhaled mannitol is a nonionic solution, unlike hypertonic saline, which is ionic. It has been proposed that the ionic nature of hypertonic saline may hinder the lung's natural antimicrobial defense.[24] Studies by Goldman et al.[26] and Smith et al.[27] demonstrated that increased concentrations of NaCl in the CF lung can lead to the inhibition of β-defensin, thus hindering the body's ability to fight infection. However, when hypertonic saline is nebulized into the airways, the sodium and chloride ions rapidly diffuse across the epithelial membrane and the transient increase in ions may not cause a clinically significant decrease in natural lung defense mechanisms.[24] Therefore, the benefit of mannitol as a nonionic agent may not be a clinically relevant advantage over ionic hypertonic saline. The rapid diffusion of NaCl in the lungs does limit the duration of osmotic effect on the ASL. Mannitol slowly diffuses across epithelial cells and thus may have a more prolonged osmotic effect than hypertonic saline.[24]

Inhaled mannitol was first compared to hypertonic saline in a noninferiority study. Inhaled mannitol was found to produce a similar degree of bronchial mucus clearance to hypertonic saline when each patient received 1 treatment (mannitol, mannitol control, NaCl 6%, NaCl 0.9%) on 4 separate days (Table 2).[24] The safety and efficacy of inhaled mannitol were established in a study comparing 420 mg inhaled mannitol twice daily versus placebo. This study demonstrated an increase in FEV_1 of 7% from baseline in the inhaled mannitol group (Table 2).[23] The sputum from the subjects in the inhaled mannitol group was evaluated and found to have decreased viscosity.[28] A

Table 1. Summary of Studies Evaluating Inhaled Hypertonic Saline in Cystic Fibrosis

Reference	Design/Population	Treatment/Duration	Results
Robinson (1997)[14]	Mucociliary clearance measurement with radioaerosol Randomized, 4-way crossover N = 10 (aged 19-28 y), FEV_1 31-84%	1 dose 0.9% NaCl + cough as controls 3% NaCl, 7% NaCl , 12% NaCl	Mucociliary clearance (%) Postintervention (30 min): 0.9% NaCl: 8.7 ± 1.7% control 3% NaCl: 13.5 ± 2.6% (p = 0.02) 7% NaCl: 15.8 ± 3.0% (p = 0.02) 12% NaCl: 17.3 ± 2.7% (p = 0.02) Postintervention (60 min) (p = 0.01): 0.9% NaCl: 12.7 ± 1.4% control 3% NaCl: 19.7 ± 3.1% (p = 0.01) 7% NaCl: 23.8 ± 4.0% (p = 0.01) 12% NaCl: 26.0 ± 3.1% (p = 0.01)
Eng (1996)[15]	Prospective, open-label, placebo-controlled, parallel-group N = 52 (aged 7-36 y), FEV_1 >40%	Twice daily 0.9% NaCl; 6% NaCl 2 wk of treatment	Change in FEV_1 from baseline at 2 wk: 0.9% NaCl: 2.8 ± 13.1% 6% NaCl: 15.0 ± 16.0% (p = 0.004) Change in FEV_1 from baseline at 4 wk: 0.9% NaCl: –2.7 ± 10.1% 6% NaCl: 0.5 ± 15.8%
Donaldson (2006)[16]	Prospective, randomized, placebo-controlled N = 24 (aged >14 y), FEV_1 >50%	4 times daily 7% NaCl + amiloride 1 mg/mL pretreatment 7% NaCl + placebo (quinine sulfate 0.25 mg/mL) pretreatment 2 wk of treatment	Mucus clearance day 14, 8-h postdose (p = 0.02): 7% NaCl + amiloride: 7.0% ± 1.5% 7% NaCl + placebo: 14% ± 2% Change in FEV_1 from baseline at 2 wk: 7% NaCl + amiloride: 2.9% (p = 0.23) 7% NaCl + placebo: 6.62% (p = 0.02)
Elkins (2006)[17]	Double-blind, parallel-group N = 164 (aged >6 y), FEV_1 >40%	Twice daily 0.9% NaCl; 7% NaCl 48 wk of treatment	Difference in linear rate of change of lung function in 7% NaCl group from 0 to 48 wk (p = 0.79): FEV_1: 0.3 mL/wk (95% CI –1.3 to 1.8) FVC: 0.5 mL/wk (95% CI –1.3 to 2.3) FEF_{25-75}: –1.5 mL/wk (95% CI –4.2 to 1.2) Absolute difference in lung function in 7% NaCl group from 4 to 48 wk (p = 0.03): FEV_1: 68 mL (95% CI 3 to 132) FVC: 82 mL (95% CI 12 to 153) FEF_{25-75}: 39 mL (95% CI –67 to 146) Mean exacerbations/pt. (p = 0.02): NaCl 0.9%: 0.89 NaCl 7%: 0.39
Dellon (2008)[18]	Open label, increasing dose n = 15 preschool children (4-7 y); n = 14 infants (4 mo-3 y) with CF; FEV_1 >60%	1 dose 3% NaCl: 8/9 preschoolers completed; 6 infants completed 7% NaCl: 7/8 preschoolers completed 8/11 infants completed	3% NaCl median change from post albuterol: Preschoolers: FEV_1: 0.04 L (p = 0.07) FVC: –0.05 L (p = 0.40) FEF_{25-75}: 0.14 L/sec (p = 0.09) Infants: $FEV_{0.5}$: –19 mL (p = 0.92) FVC: –9 mL (p = 0.92) FEF_{25-75}: –61 mL/sec (p = 0.60) 7% NaCl median change from post albuterol: Preschoolers: FEV_1: –0.25 L (p = 0.02) FVC: –0.24 L (p = 0.15) FEF_{25-75}: –0.16 L/sec (p = 0.35) Infants: $FEV_{0.5}$: 15 mL (p = 0.14) FVC: 25 mL (p = 0.36) FEF_{25-75}: 32 mL/sec (p = 0.21)

CF = cystic fibrosis; FEF_{25-75} = forced expiratory flow at 25-75% vital capacity; $FEV_{0.5}$ = forced expiratory volume in 0.5 seconds; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

recently completed Phase 3 study compared inhaled mannitol 400 mg twice daily versus placebo for 26 weeks. The preliminary results demonstrated an increase in FEV_1 of 122 mL from baseline, which was statistically significant ($p < 0.001$) compared to placebo. This study also evaluated subjects treated with rhDNase therapy in conjunction with mannitol. When these subjects were compared to their respective placebo group, there was a statistically significant increase in FEV_1 ($p = 0.002$) (Table 2).[29] In contrast to the pulmonary function improvement shown by Bilton et al.,[29] a study by Minasian et al.[25] showed a negative effect on FEV_1 when the 2 agents were combined, (Table 2). The study was completed by 20 children receiving mannitol 400 mg inhaled twice daily, rhDNase 2.5 mg inhaled twice daily, or combination treatment for 12 weeks. The study demonstrated similar improvements in FEV_1 between the mannitol (6.7%) and rhDNase (7.2%) groups; however, the combination group demonstrated only a 1.9% increase in FEV_1, which did not reach statistical significance ($p = 0.67$). The data in this crossover trial did suggest that patients demonstrating minimal or no benefit with rhDNase therapy alone may benefit from switching to mannitol therapy but not with the addition of mannitol to rhDNase therapy. It was hypothesized that there could be a lack of adherence to combination therapy, leading to administration of less than therapeutic doses, or that the combination could reduce mucus viscosity to a degree that effective mucociliary clearance would be hindered.[25] There was a sig-

Table 2. Summary of Studies Evaluating Inhaled Mannitol in Cystic Fibrosis

Reference	Design/Population	Treatment/Duration	Results
Robinson (1999)[24]	Bronchial mucus clearance measured by radioaerosol and gamma camera N = 12 (aged 16-46 y), FEV_1 >40% Each pt. received 1 treatment on 4 days: day 1: inhaled mannitol; day 2: inhaled mannitol control; day 3: NaCl 6%; day 4: 0.9% NaCl	Inhaled mannitol 300 mg Inhaled mannitol control + matched cough NaCl 6% NaCl 0.9% control + matched cough	Mucus clearance Postintervention (60 min) mannitol: 8.7 ± 3.3% (p = 0.01) mannitol control: 2.8 ± 0.7% NaCl 6%: 10.0 ± 2.3% (p = 0.01) NaCl 0.9% control: 3.5 ± 0.8% Cough clearance (30 min) mannitol: 9.7 ± 2.4% (p = 0.001) mannitol control: 2.5 ± 0.8% NaCl 6%: 9.9 ± 2.7% NaCl 0.9% control: 6.1 ± 1.6%
Jaques (2008)[23]	Randomized, double-blind, placebo-controlled, crossover N = 49 (aged 8-48 y), FEV_1 41-91%	Inhaled mannitol 420 mg twice daily Placebo (nonrespirable mannitol: fine particle fraction <2%) twice daily Treatment for 2 wk with 2-wk washout between crossover	Relative change in FEV_1 from baseline: mannitol: 7.0% (p < 0.001) placebo: 0.3% (p < 0.01) Relative change in FEF_{25-75} from baseline: mannitol: 15.5% (95% CI –6.5 to 24.6) placebo: 0.7% (95% CI –8.3 to 9.7) Relative change in FEV_1/FVC from baseline: mannitol: 2.2% (p < 0.05) placebo: –0.8%
Bilton (2009)[29]	Randomized, double-blind, placebo-controlled N = 295 (aged >6 y), FEV_1 30-90%	Mannitol 400 mg inhaled twice daily Placebo (nonrespirable mannitol: fine particle fraction <2%) inhaled twice daily 26 wk	Change in FEV_1 from baseline at 26 wk: mannitol: 122 mL (p < 0.001) placebo: 25 mL Change in FEV_1 from baseline at 14 wk: mannitol: 97 mL (p < 0.001) placebo: 20 mL Change in FEV_1 from baseline at 26 wk: mannitol + rhDNase: 96.2 mL (5.2%) (p = 0.002 vs placebo)
Minasian (2010)[25]	Prospective, randomized, open-label, crossover N = 20 (aged 8-18 y), FEV_1 40-70%	Mannitol 400 mg inhaled twice daily rhDNase 2.5 mg inhaled twice daily Mannitol 400 mg inhaled twice daily + rhDNase 2.5 inhaled twice daily 12-wk treatment blocks with 2-wk washout periods	Change in FEV_1 between treatments from baseline: mannitol: 0.11 L (6.7%) (p = 0.055) rhDNase: 0.12 L (7.2%) (p = 0.03) mannitol + rhDNase: 0.03 L (1.9%) (p = 0.67) Change in FEV_1 between treatments adjusted for baseline: mannitol: 2.8% (p = 0.42) mannitol + rhDNase: –4.3% (p = 0.4) Change in FVC between treatments adjusted for baseline: mannitol: 0.14% (p = 0.053) mannitol + rhDNase: –0.07% (p = 0.52) Change in FEF_{25-75} between treatments adjusted for baseline: mannitol: –0.01% (p = 0.91) mannitol + rhDNase: 0.03% (p = 0.76)

FEF_{25-75} = forced expiratory flow at 25-75% vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

nificant attrition rate (47%), which was attributed to bronchoconstriction and troublesome cough reported with inhaled mannitol treatment.[25] A larger, blinded study is needed with the combination of rhDNase and mannitol to determine whether there is additive benefit from the combination in pediatric patients, as this study was not adequately powered to detect a difference.

Comparative studies of the effect of inhaled mannitol on pulmonary function have demonstrated its equivalence to hypertonic saline, leading to the evaluation of these agents on the basis of administration and tolerability (Table 3). Nebulized hypertonic saline takes approximately 15 minutes to administer per 4-mL dose with the Pari LC nebulizer. Inhaled mannitol, as a dry powder capsule formulation, can be administered in approximately 3-5 minutes.[23] This appreciable time savings would be beneficial for patients who already have a high medication administration time burden. As a dry powder inhaler, mannitol will also be more portable for patients, thus making it a more attractive option. Currently, inhaled mannitol is available for clinical trials in 40-mg capsules; therefore, to receive a 400-mg dose, patients must inhale the contents of 10 capsules. This may initially be very overwhelming to patients; while time of inhalation may decrease with practice, this will still be inconvenient for them (Table 3).

The most common adverse effect observed with inhaled mannitol is cough, with an incidence similar to that of hypertonic saline; however, inhaled mannitol has produced concerning bronchoconstriction in some patients with CF.[23,25] Cough may be beneficial for patients, helping them to expectorate mucus; however, as with hypertonic saline, pretreatment with an inhaled bronchodilator is prudent. In 2 pediatric inhaled mannitol studies, it was suggested that a lower dose of inhaled mannitol may be helpful to reduce bronchospasm, increase medication adherence, and increase tolerability in this patient population.[25,30] However, mannitol 400 mg inhaled twice daily has been studied in large trials that included some pediatric patients in whom this dose was well tolerated.[23,29] A positive dose response has been demonstrated in adults with bronchiectasis with increasing mannitol doses up to 480 mg.[31] Based on these findings, it is probable that dosage reduction may be considered for patients who cannot tolerate the higher mannitol dose.

Inhaled mannitol is a promising airway-rehydrating agent as a potential alternative to hypertonic saline treatment. It is unclear whether this agent should be combined with rhDNase due to conflicting evidence.[25,29] Increased cough/bronchoconstriction is significant with this agent and pretreatment with a bronchodilator should occur before each dose. The dry powder formulation of inhaled mannitol increases portability and decreases time of administration compared with hypertonic saline (Table 3). The benefits of inhaled mannitol may have a positive effect on patient adherence to airway rehydrating treatment, although cost and tolerability will certainly be a factor.

Denufosol

Denufosol is a puridinine triphosphate derivative investigational $P2Y_2$ receptor agonist administered by nebulization and currently in Phase 3 trials for use in patients with CF. This $P2Y_2$ agonist stimulates a calcium-activated chloride channel on the airway epithelia, allowing chloride to flow into the ASL, thus bypassing the malfunctioning CFTR protein-regulated chloride channel (Figure 2).[32] In animal studies, denufosol increased chloride and water secretion in the airways of chimpanzees.[32] Denufosol increases goblet-cell degranulation leading to mucin production, which traps foreign particles in the lungs. An increase in mucociliary clearance has been reported with denufosol

Table 3. Comparison of Inhaled Mannitol and Hypertonic Saline

Inhaled Mannitol	Hypertonic Saline
Dry powder inhaler	Nebulized solution
Administration time: 3-5 min	Administration time: 15 min
Portable	Portability limited by size of nebulizer
Requires coordination of breath for inhalation	Does not require coordination of breath for inhalation

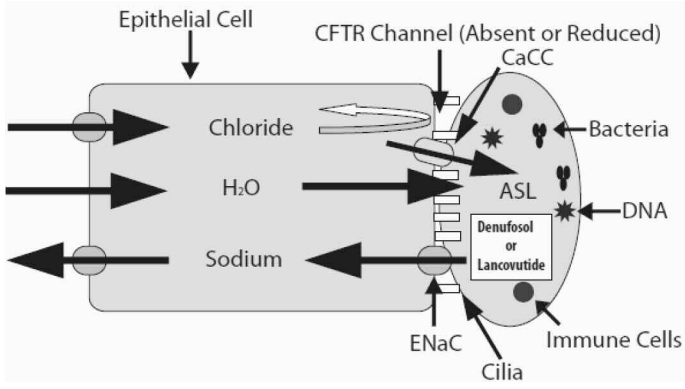

Figure 2. Schematic of water and sodium chloride transport in the epithelial cell of the cystic fibrosis airway following nebulization of denufosol or lancovutide. Denufosol stimulates the $P2Y_2$ receptor, allowing chloride to flow through the CaCC into the ASL, increasing the amount of fluid. Lancovutide, like denufosol, activates the CaCC, allowing chloride to flow into the ASL. Lancovutide activates this channel by increasing intracellular calcium through the release of calcium from endoplasmic reticulum stores. ASL = airway surface liquid; CaCC = calcium-activated chloride channel with $P2Y_2$ receptors; CFTR = cystic fibrosis transmembrane conductance regulator; ENaC = epithelial sodium channel.

in patients with chronic obstructive pulmonary disease.[33] The increased mucociliary clearance is attributed to the increased hydration of the ASL and the ability of denufosol to increase ciliary beating. Pharmacokinetic studies of denufosol have demonstrated that 18% of a nebulized dose reached the lungs and only 2.6% reached the systemic circulation; it was then rapidly metabolized, thus reducing the risk for systemic adverse effects.[33]

The safety and tolerability of denufosol were established in 3 dose-finding studies investigating dosages of 10, 20, 40, and 60 mg (Table 4).[34-36] All 3 studies concluded that denufosol was well tolerated at doses up to 60 mg 3 times daily. In the 2007 study by Deterding et al.,[36] both denufosol 20 mg and 60 mg produced statistically significant increases in FEV_1 and forced expiratory flow at 25-75% vital capacity. All doses of denufosol were expected to exceed the maximally effective concentration on the airway surface based on nasal potential difference studies. Despite beneficial effects and fewer adverse effects with denufosol 20 mg, denufosol 60 mg 3 times a day was selected for Phase 3 trials. The absolute changes in the results of pulmonary function tests were small during the short study period; however, they showed that the drug may help maintain improved pulmonary function for a longer time in patients with mild lung involvement. The results of these 3 studies also demonstrated slight decreases in exacerbation rates. Adverse effects reported in these studies included cough, chest tightness, wheezing, and increased sputum.[34-36]

A Phase 3 trial of denufosol, TIGER-1 (Transporting Ion Generating Epithelia Rehydration), compared denufosol 60 mg 3 times a day versus placebo for 24 weeks. The subjects (≥5 years old) had relatively good lung function, with FEV_1 ≥75%. The results of this study demonstrated an increase in FEV_1 of 48 mL, which was statistically significant (p = 0.047), but produced no significant difference in pulmonary exacerbation rates (Table 4).[37]

It is still unclear whether the increase in FEV_1 observed in TIGER-1, which is small numerically, will have a clinical impact. The data from the 24-week open-label extension of TIGER-1 suggest that FEV_1 continues to increase

Table 4. Summary of Studies Evaluating Inhaled Denufosol in Cystic Fibrosis

Reference	Design/Population	Treatment/Duration	Results
Deterding (2005)[34]	Double-blind, randomized, multicenter N = 61 (adults: ≥18 y; pediatrics: 5-17 y) Pts. randomized in cohorts: cohorts 1-2: FEV_1 ≥50% cohort 3: FEV_1 40-70%	Part I: ascending doses of denufosol 10, 20, 40, 60 mg, or placebo (0.9% NaCl) Part II: maximum tolerated dose twice daily for 5 days	Pts. reaching maximum tolerated dose for cohort: adult denufosol: 23 (82%) adult placebo: 8 (89%) pediatric denufosol: 16 (89%) pediatric placebo: 5 (83%) Maximum tolerated dose: 60 mg
Smiley (2006)[35] (abstract only)	Placebo-controlled, randomized, multicenter study N = 72 (aged 8-50 y) FEV_1 60-90%	Denufosol 20 mg 3 times daily Denufosol 60 mg 3 times daily Placebo 3 times daily (0.9% NaCl)	Change from baseline vs placebo: denufosol combined FEV_1: 2.4% denufosol combined FEF_{25-75}: 5.9% Pulmonary exacerbation rate: denufosol combined: 4% placebo: 7%
Deterding (2007)[36]	Double-blind, randomized, placebo-controlled, parallel-group, multicenter N = 89 (aged 8-50 y) FEV_1 ≥75%	Denufosol 20 mg 3 times daily Denufosol 40 mg 3 times daily Denufosol 60 mg 3 times daily Placebo 3 times daily (0.9% NaCl) 28 days	Adjusted mean FEV_1 change from baseline vs placebo: denufosol 20 mg: 0.18 (p = 0.004) denufosol 40 mg: 0.09 (p = 0.135) denufosol 60 mg: 0.15 (p = 0.021) combined denufosol: 0.14 (p = 0.006) Adjusted mean FEF_{25-75} change from baseline vs placebo: denufosol 20 mg: 0.40 (p = 0.004) denufosol 40 mg: 0.19 (p = 0.178) denufosol 60 mg: 0.30 (p = 0.031) combined denufosol: 0.30 (p = 0.008) Exacerbation rate: placebo: 10% denufosol 20 mg: 4% denufosol 40 mg: 9% denufosol 60 mg: 0%
Moss (2009)[37] (TIGER-1)	Double-blind, placebo-controlled, randomized, multicenter N = 352 (age ≥5 y) FEV_1 ≥75%	Denufosol 60 mg 3 times daily Placebo 3 times daily (0.9% NaCl) 24 wk + 24-wk open-label extension	Mean FEV_1 change from baseline to 24 wk: placebo: 3 mL denufosol: 48 mL (p = 0.047) Mean FEV_1 change from baseline to 48 wk: denufosol: 115 mL (6.1%) Exacerbation rate: placebo: 51 (29%) denufosol: 61 (34%)

FEF_{25-75} = forced expiratory flow at 25-75% vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

with continued use of denufosol. Even if the FEV_1 increase was relatively small over the 24-week treatment period, it could result in a substantial increase over time. An additional 48-week study of denufosol (TIGER-2) is currently ongoing.[37] The results of this study may further define the clinical significance of denufosol's effect on lung function.

Denufosol has a unique mechanism of action that is designed to bypass the basic chloride exchange defect present in the CF lung. In addition to increasing the volume of ASL, denufosol also increases surfactant release, mucin, and mucociliary clearance. Although a logical combination mechanistically, it is unclear whether denufosol will be synergistic or antagonistic with hypertonic saline since combination therapy has not been evaluated. Denufosol used in clinical trials is produced as a 4-mL, unit-dose solution for nebulization to be administered with a Pari LC Star jet nebulizer 3 times daily, taking approximately 15 minutes to nebulize 1 dose. The 3 times daily dosing schedule is a potential drawback to adherence to the already large nebulized medication burden of the typical patient with CF. Denufosol is a promising airway-rehydrating agent, but further evaluative studies and eventual cost will be needed to determine its exact role in CF therapy.

Lancovutide (Moli1901)

Lancovutide is a stable 19-residue polycyclic peptide being investigated as an airway-rehydrating agent for use in CF. Its mechanism of action is similar to that of denufosol in that it activates an alternative chloride channel (Figure 2). However, lancovutide activates this channel by increasing intracellular calcium, releasing it from storage sites in the endoplasmic reticulum.[38]

A pilot study on the effect of intranasal lancovutide assessed potential differences in healthy participants compared with patients with CF. The investigators found that the healthy volunteers exhibited a dose-related increase in chloride transport in the nasal mucosa; however, the increase in the CF population was not clearly dose related (Table 5).[39] A Phase 2 study of lancovutide inhalation at doses of 0.5, 1.5, and 2.5 mg for 5 days demonstrated that the agent was well tolerated. There was a dose response increase in FEV_1 from baseline in this short study and the increase was sustained at 26 days in the 2.5-mg treatment group. Adverse effects reported were throat numbness, headache, chest discomfort, and gastrointestinal discomfort (Table 5).[40] Lancovutide 2.5 mg inhaled daily for 28

Table 5. Summary of Studies Evaluating Lancovutide (Moli1901) in Cystic Fibrosis

Reference	Design/Population	Treatment/Duration	Results
Zeitlin (2004)[39]	Randomized, placebo-controlled, single-blind n = 4 (healthy subjects, aged 18-40 y); n = 4 (pts. with CF, age ≥18 y) FEV_1 ≥ 60%	Nasal potential difference: lancovutide (Moli1901) 0.01, 0.03, 0.1, 0.3, 1, 3, 10 µM Vehicle	Non-CF: lancovutide increased chloride transport compared vs vehicle at 1, 3, and 10 µM Dose response in CF: lancovutide increased chloride transport at 3 µM; variable dose response; solutions up to 10 µM were well tolerated
Grasemann (2007)[40]	Placebo-controlled, double-blind, single-center, multiple, rising-dose 3 cohorts of 8 pts. (aged ≥16 y) FEV_1 ≥ 60%	Cohort 1: lancovutide 0.5 mg daily Cohort 2: lancovutide 1.5 mg daily Cohort 3: lancovutide 2.5 mg daily placebo (0.9% NaCl) 5 days	Mean FEV_1 change from baseline to day 5 (p = 0.027): placebo: –2.5% lancovutide 0.5 mg: 2% lancovutide 1.5 mg: 6% lancovutide 2.5 mg: 7% Mean FEV_1 change from baseline to day 26 (p = 0.023): placebo: –1% lancovutide 0.5 mg: –8.5% lancovutide 1.5 mg: 2% lancovutide 2.5 mg: 8% Mean FEF_{25-75} change from baseline to day 5: placebo: –3.5% lancovutide 0.5 mg: 0.5% lancovutide 1.5 mg: 7% lancovutide 2.5 mg: 5% Mean FEF_{25-75} change from baseline to day 26: (p = 0.053): placebo: –11% lancovutide 0.5 mg: –12% lancovutide 1.5 mg: 1% lancovutide 2.5 mg: 1%
Lantibio (2009)[41]	Multicenter, once-daily dosing n = 9 (aged ≥16 y); n = 9 (aged 12-16 y)	Lancovutide 2.5 mg daily Placebo (0.9% NaCl) 28 days	Mean FEV_1 change from baseline to day 56: placebo: –3% lancovutide 2.5 mg: 2% (p = 0.0217)

CF = cystic fibrosis; FEF_{25-75} = forced expiratory flow at 25-75% vital capacity; FEV_1 = forced expiratory volume in 1 second.

days was assessed in patients with CF older than 12 years. Treatment was well tolerated and there was a statistically significant increase ($p = 0.0217$) in FEV_1 in the lancovutide group (Table 5).[41] A recently completed dose-finding study compared lancovutide 2.5 mL daily, every other day, and twice weekly to placebo for 8 weeks in patients with CF older than 12 years with FEV_1 50-85%. Results for this study have not been published but will help determine the dose of lancovutide to be used in Phase 3 studies.[42]

Lancovutide, like denufosol, has the potential to bypass the CFTR defect and increase ASL. Lancovutide will be a nebulization solution, but the exact dose and frequency have not been determined. Lancovutide is being used in studies as a 5-mL solution nebulized with the PARI LC Plus nebulizer, with an approximately 15- to 20-minute nebulization time.[40] Preliminary studies suggest that lancovutide may have a long duration of action in the lungs, which may allow less-frequent dosing. If approved and cost competitive, it may be an alternative to denufosol.

Summary

Hypertonic saline is currently the only commercially available airway-rehydrating agent for CF. New drugs being evaluated may compete with hypertonic saline or perhaps be additive. Some of these drugs are close to approval, such as denufosol and inhaled mannitol; lancovutide is only in early-phase studies. Inhaled mannitol is positioned to be an alternative to hypertonic saline. Inhaled mannitol has benefits over hypertonic saline for patients who need increased portability due to its dry powdered formulation. Denufosol and lancovutide have unique mechanisms of action that have the ability to bypass the basic CFTR defect. These agents could be additive with hypertonic saline therapy; however, current studies have not evaluated this combination. Denufosol and lancovutide are both nebulizer solutions that take approximately 15-20 minutes to administer. Denufosol is dosed 3 times a day, which may adversely affect patient adherence. These new airway-rehydrating agents may help modify the course of CF lung disease, thus increasing patient outcomes and quality of life. Comparison of dosage schedule, administration method, administration time, patient adherence, and cost will be important factors to consider in the selection of airway-rehydrating agents for patients with CF.

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Agentes Re-Hidratantes de las Vías Aéreas Para el Tratamiento de Fibrosis Quística: Pasado, Presente, y Futuro

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EXTRACTO

OBJETIVO: Revisar y evaluar los agentes re-hidratantes de las vías aéreas que se usan en el tratamiento de fibrosis quística (CF).

FUENTES DE INFORMACIÓN: Revisión bibliográfica de la literatura usando MEDLINE (1977–agosto 2010), Biblioteca Cochrane, e *Abstractos Farmacéuticos Internacionales* (1977–agosto 2010). Los términos de búsqueda fueron salina hipertónica, manitol inhalado, denufosol, Moli1901, lancovutida, y fibrosis quística. Las fichas de referencia de algunos artículos fueron revisadas.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Todos los artículos en inglés identificados de las fuentes de información fueron evaluados para inclusión. Estudios clínicos en humanos y artículos de revisión relevantes fueron evaluados para cada agente re-hidratante de las vías aéreas.

SÍNTESIS: El área de agentes re-hidratantes de las vías aéreas es una que se está expandiendo. La salina hipertónica es actualmente el único agente re-hidratante de las vías aéreas que está comercialmente disponible para la terapia crónica de pacientes con CF y está siendo evaluada como tratamiento en pacientes jóvenes. El manitol inhalado es un agente bajo investigación de inhalación en polvo que mejora la depuración de la mucosidad de forma similar a la salina hipertónica y produjo un aumento estadísticamente significativo en FEV1 en un estudio clínico fase 3. Denufosol, un agonista P2Y2, rehidrata el líquido superficial de las vías aéreas (ASL) circunvalando el defecto de la proteína reguladora conductora transmembrana (CFTR) básica de la CF. Produce una mejoría en las pruebas de función pulmonar y está siendo investigado en un estudio clínico fase 3. Lancovutida (Moli1901) es un agente en etapas tempranas de investigación que activa un canal de cloro dependiente de calcio que permite que el cloro entre a las vías aéreas.

CONCLUSIONES: La salina hipertónica es actualmente el agente re-hidratante de las vías aéreas principal que se usa en el tratamiento de CF. El manitol inhalado puede ser una alternativa a la salina hipertónica debido a que es más rápido y fácil de administrar. No queda claro si denufosol y lancovutide serán sinergísticos o antagonistas en combinación con salina hipertónica. Ambos agentes tienen un mecanismo de acción único el cual circunvala el defecto básico de la CFTR. La gama de agentes rehidratantes de las vías aéreas se está expandiendo con la esperanza que mejorará la calidad de vida para los pacientes con CF.

Traducido por Homero A Monsanto

Les Agents Fluidifiants Bronchiques Pour le Traitement de la Fibrose du Pancréas (Muciviscidose): le Passé, le Présent, et le Futur

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RÉSUMÉ

OBJECTIF: Revoir et évaluer les agents fluidifiants bronchiques utilisés pour le traitement de la fibrose du pancréas (mucoviscidose).

REVUE DE LA LITTÉRATURE: Les articles pertinents ont été identifiés à l'aide d'une recherche dans la banque de données informatisée MEDLINE (1977-août 2010), Cochrane Library et dans *International Pharmaceutique Résumé* (1977-août 2010) en utilisant les mots solution saline hypertonique, mannitol pour inhalation, denufosol, Moli 1901, lancovutide et fibrose du pancréas. Les références bibliographiques d'intérêt citées dans ces articles ont aussi été revisées.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Tous les articles publiés en anglais et identifiés par cette recherche ont été évalués pour inclusion. Les essais cliniques chez les humains et les articles de revue pertinents ont été évalués pour chaque agent fluidifiant bronchique.

RÉSUMÉ: Les agents fluidifiants bronchiques pour le traitement de la fibrose du pancréas constituent une option de traitement en expansion. La solution saline hypertonique est actuellement le seul agent fluidifiant disponible commercialement et recommandé pour le traitement chronique des patients avec fibrose du pancréas et est en évaluation chez les jeunes patients. Le mannitol pour inhalation est un agent en poudre pour inhalation en investigation qui améliore la clairance du mucus de la même façon que la solution saline hypertonique. Dans un essai de phase 3, il a produit une amélioration significative de la fonction respiratoire mesurée par le FEV1. Le denufosol, un agoniste P2Y2, hydrate le film à la surface des bronches en contournant la dysfonction de la protéine CFTR (cystic fibrosis transmembrane conductance regulator); la protéine CFTR est un canal chlorique présent dans les épithéliums de la plupart des lumières de l'organisme et est un facteur contributoire significatif de l'équilibre sodique et hydrique. Le denufosol améliore les tests de fonction respiratoire et fait l'objet d'un essai clinique de phase 3. Le lancovutide (Moli 1901) est un agent qui fait l'objet de recherche dans les toutes premières phases; il active le canal chlorique calcium-dépendant permettant au chlore d'entrer dans les bronches.

CONCLUSIONS: La solution saline hypertonique est actuellement l'agent fluidifiant bronchique de première intention utilisé pour le traitement de la fibrose du pancréas. Le mannitol pour inhalation pourrait devenir une autre option car son administration est plus facile et plus rapide. Il reste à préciser si le denufosol et le lancovutide seront synergiques ou antagonistes de l'action de la solution saline hypertonique. Ces 2 agents ont un mécanisme d'action unique qui contourne le défaut génétique de dysfonction de la protéine CFTR. Le groupe des agents fluidifiants bronchiques disponibles est en expansion et il est à souhaiter que ces agents permmettront l'amélioration de la qualité des soins donnée aux patients ayant la fibrose du pancréas.

Traduit par Denyse Demers