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Aerosolized Dornase Alfa in Cystic Fibrosis: Is There a Role in the Management of Patients With Early Obstructive Lung Disease?

David E. Geller, MD*

Summary. Airway inflammation and infection are present in patients with mild lung disease in cystic fibrosis (CF), suggesting the need for early treatment. In a previously reported large multicenter trial, dornase alfa improved pulmonary function and decreased the need for hospitalization in patients with CF over 5 years of age and with forced vital capacity greater than 40% predicted. We report here preliminary results of a study of dornase alfa delivered by two different nebulizer systems to patients with mild lung disease in CF and near normal lung function. Even in this mild group dornase alfa improved pulmonary function. The delivery system with the smaller droplet size tended to provide greater improvement than the system with the larger droplet size, although this difference was not statistically significant. We have reviewed characteristics of nebulizers and patients' lung function that might affect efficacy of different nebulizer delivery systems. Our results indicate that treatment can improve pulmonary function in patients with mild lung disease in CF and illustrate the need for further studies in this group of patients. **Pediatr. Pulmonol. 1997; 24:155–158.**

Key words: cystic fibrosis; lung function testing; aerosol; nebulization; dornase alfa.

INTRODUCTION

The evidence for the early onset of inflammation in CF lung disease has been highlighted in a number of recent publications.[1–3] Dr. Konstan (this volume) has reviewed the current status of our knowledge. Whatever the relationship between infection and inflammation, it is clear that large numbers of neutrophils are present in the airways of even the youngest CF patients.[1,2] Degenerating neutrophils in the airways release large amounts of DNA, which contributes to increased viscoelasticity of sputum in CF.[4] rhDNase (dornase alfa) reduces this viscoelasticity in vitro by hydrolyzing the large amounts of extracellular DNA.[5] In CF patients, dornase alpha improves pulmonary function and reduces the frequency of those respiratory tract exacerbations that require intravenous antibiotics.[6] The purpose of this paper is to review the evidence suggesting that patients with early spirometric evidence of airway obstruction respond to dornase alpha therapy and to discuss the way in which delivery of dornase alfa might be optimized in these patients.

REVIEW OF METHODS IN USE

Figure 1 illustrates the important characteristics of a typical jet nebulizer. The drug solution to be aerosolized is placed in the nebulizer cup and is referred to as the ''nominal'' dose. Compressed air is driven through a Venturi chamber, and a spray of drug is directed through a baffle system, producing a fine aerosol with particles of varying sizes. Not all the droplets exit the nebulizer chamber, resulting in unused drug or *dead volume*, which varies with the nebulizer system but may be as high as 50%.[7] The proportion of nebulized drug that leaves the chamber is the *efficiency* of the system, expressed as the percentage of the nominal dose available to the patient. Aerosols consist of particles of varying sizes. Particle size determines whether an aerosol is deposited on the epithelial surface of the lower airway. Droplets are deposited by one of three mechanisms: impaction, sedimentation (gravity), and diffusion.[8] The larger the particle the more likely it is to impact in the throat or at bifurcation points in the airway. Generally, particles larger than 6 μm are likely to impact in the upper airway and thus would be of little use if the target is the lower airway. Smaller particles are able to penetrate deeper into the airways, ultimately depositing on the airway wall by gravitational forces as their speed slows in the peripheral

Division of Pulmonology, The Nemours Children's Clinic, Orlando, Florida.

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*Correspondence to: Dr. D.E. Geller, The Nemours Children's Clinic, Division of Pulmonology, 85 West Miller Street, Suite 203, Orlando, FL 32806.

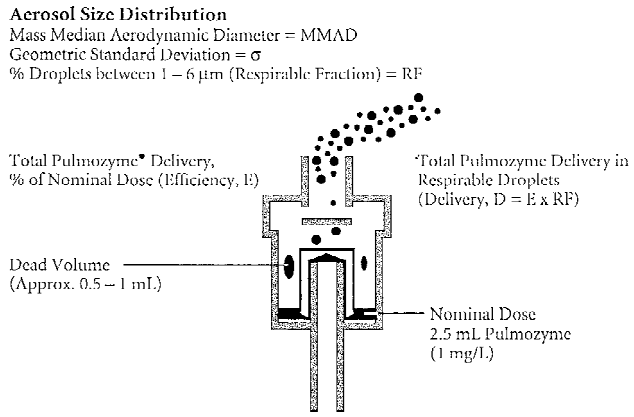

Fig. 1. Diagrammatic representation of jet nebulizer output, with nebulizer characteristics defined. (Modified from Clarke and Pavia.[8])

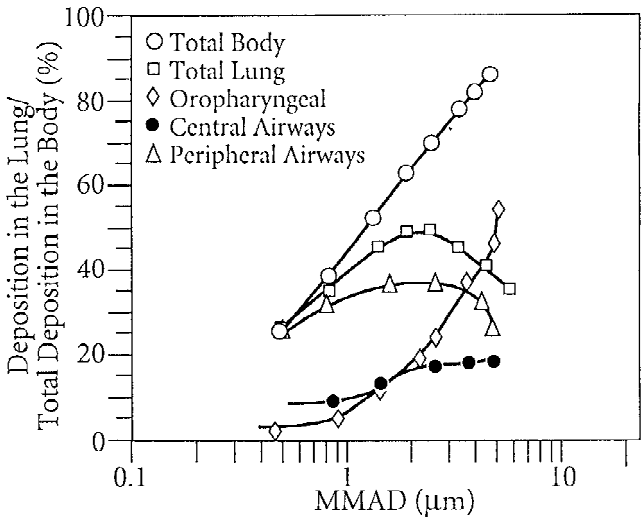

Fig. 2. Aerosol deposition in the airway as a function of aerosol particle size. (Modified from Rudolf et al.[7])

airways. Submicronic particles are more likely to deposit by diffusion, or be exhaled. This has implications for the targeting of aerosols to specific regions of the lung. Figure 2 shows a compilation of work indicating the deposition of aerosol particles at specific sites in the airway as a function of particle size.[7]

Particle size distribution of an aerosol is expressed as the MMAD in microns. The percentage of droplets delivered from a nebulizer that are within the range of 1–6 μm is termed the *respirable fraction.* Thus, the total respirable delivery of any aerosolized drug that is available to the intrathoracic airways is a function of *efficiency* and the *respirable fraction.* These parameters are highly variable from system to system, even within different manufacturing batches of the same system. For jet nebulizers, *respirable fraction* ranges from as low as 10% to as high as 50% of the nominal dose.[9] Thus, it seems reasonable to suppose that variances in the characteristics of nebulizer systems could affect aerosolized drug delivery.

Hardy and coworkers[10] showed that when particle size was reduced to the lower end of the respirable range, the deposition of drug to the peripheral airways was nearly doubled compared with a larger particle size. This is also true in studies of aerosolized bronchodilators in which smaller particle aerosols result in greater bronchodilator effects than large particle aerosols.[11,12] This observation has also been confirmed under experimental conditions where improved penetration and peripheral deposition was achieved by reducing particle size.[13,14] Similarly, there is evidence that patient characteristics affect aerosol deposition. This may influence the response to aerosolized medications and may be especially important when considering the response of different patients to dornase alfa.

In its earliest stages CF is characterized by obstruction of the smaller airways.[15] With progression of disease, obstruction is more readily apparent in the central airways. This is illustrated by the progression of detectable spirometric changes from the most sensitive parameter of maximum midexpiratory flow in early disease to evidence of reduced FVC in advanced cases. Increasing severity of disease has implications for aerosolized drug delivery. Alderson and coworkers[16] demonstrated that increased severity of CF lung disease reduced the peripheral delivery of aerosolized radiolabeled technetium albumin. Patients with greater degrees of obstructive lung disease and areas of poor ventilation had lower aerosolized drug delivery. These findings were confirmed by the work of Laube et al.,[17] who showed in asthmatic subjects that radioaerosol clearance was inversely correlated with the baseline FEV_1. These data suggest that the magnitude of bronchial obstruction determines aerosol distribution within the lung, and that increased bronchial obstruction enhances central airway deposition of inhaled particles. Ilowite and his collaborators[18] performed similar studies in CF patients using a small particle nebulizer to assess gentamicin delivery (Fig. 3). They found that an inverse relationship existed between the ratio of centrally to peripherally distributed drug and percentage of FEV_1. Thus, in patients with a higher FEV_1 and therefore milder disease, there was a greater tendency for peripheral drug delivery using the small particle aerosol system.

Abbreviations

CF	Cystic fibrosis
$FEF_{25–75}$	Forced expired flow between 25% and 75% of vital capacity
FEV_1	Forced expired volume in 1 second
FVC	Forced vital capacity
MMAD	Mass median aerodynamic diameter
rhDNase	Dornase alfa

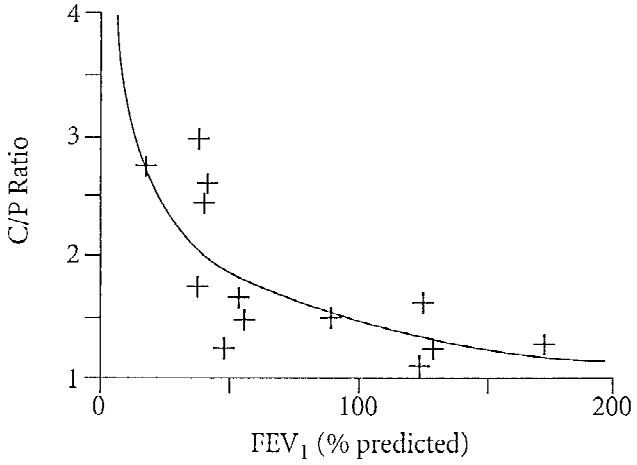

Fig. 3. Effect of pulmonary function on central versus peripheral aerosol deposition. FEV_1 (as % of predicted) is plotted against central/peripheral ratios. A hyperbolic relationship was seen (r = 0.76, $P < 0.05$), i.e., the more obstructed the patient as assessed by FEV_1, the more central the aerosol distribution. (Modified from Ilowite et al.[18])

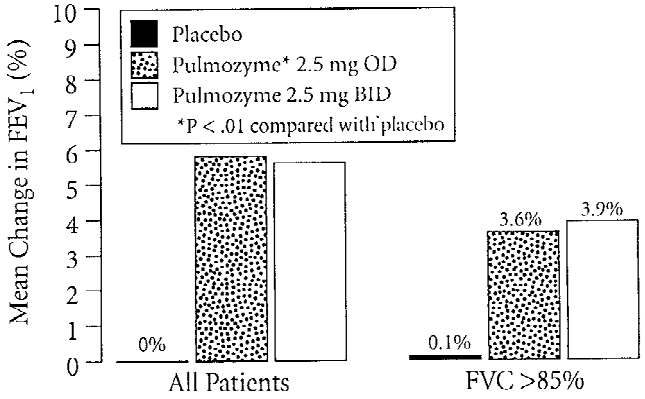

Fig. 4. Improvement in pulmonary function (% change from baseline in FEV_1) for patients in the pivotal 6 month Phase III study of rhDNase. Left panel, all patients. Right panel, patients with a baseline FVC of greater than 85% of prediction for age, sex, and weight (data on file with Genentech, Inc.)

DORNASE ALFA

Aerosolized Dornase Alfa

There is abundant evidence that patients with evidence of early obstructive lung disease demonstrate improvement in pulmonary function with aerosolized dornase alfa. The mean baseline values for FVC and FEV_1 of the 968 CF patients recruited into the Phase III pivotal study of dornase alfa were 78% and 61%, respectively. In this group a cohort of 370 was identified that had a baseline FVC of greater than 85% of their predicted value for age and height. These were evenly distributed within the three treatment groups (placebo and dornase alfa 2.5 mg once daily and 2.5 mg twice daily). The response of these patients to dornase alfa was the same as the response of the whole study population. Compared with placebo, there was a statistically significant improvement in FVC, FEV_1 and $FEF_{25–75}$ (Fig. 4). Similarly, the incidence of respiratory tract exacerbations was reduced in this group of patients, even though these events occurred much less frequently than in the whole study population because of their relatively mild CF. These studies were performed with a nebulizer system (Hudson T Up-draft II, powered with a Pulmo-Aide compressor), which delivers a MMAD of dornase alfa of approximately 5 μm. The respirable fraction of this system is approximately 25%. Earlier studies of dornase alfa in CF had shown greater improvements in FEV_1 and had been conducted with a different system (Acorn II, powered by the Pulmo-Aide compressor).[19] This system had very similar characteristics in terms of delivery and particle size. A subsequent study that directly compared these two systems and another system with almost identical characteristics (Pari LC-plus) showed no differences in pulmonary function response between groups of CF patients with moderate airway obstruction.[20]

Other Delivery Systems

Some question remains about nebulizer systems with different in vitro characteristics. Recently the group from the Brompton Hospital in London showed that alterations in the delivery characteristics of nebulized dornase alfa can influence the response as measured by spirometry.[21] Shah and coworkers[21] recruited 173 patients to receive dornase alfa either via a Hudson T Up-draft II with a Pulmo-Aide compressor or the Durable Sidestream nebulizer, powered by a CR50 compressor. The systems differed in their delivery characteristics. The Sidestream nebulizer had a faster nebulization rate ($P < 0.05$), lower MMAD ($P < 0.001$), and higher percentage of particles in the respirable range ($P < 0.001$). No statistically significant differences in patient response were seen between the two systems, but a trend toward a greater improvement in FEV_1 was seen in the group receiving the smaller particle size aerosol (16% versus 11.4%, $P = 0.14$).

Dornase Alfa in Patients With Early Lung Disease

To examine prospectively the response to dornase alfa in CF patients with early obstructive lung disease, we examined the effects of differences in aerosol particle size on pulmonary function response in a group of stable CF patients with an FVC of 70% predicted or greater.[22] A total of 749 patients were recruited at 40 U.S. and Canadian sites. Patients received 2.5 mg dornase alfa daily for 14 days and were randomized to one of the

nebulizer systems (Hudson-T Up-draft II with Pulmo-Aide, or Durable Sidestream with MobilAire). The two nebulizer systems were significantly different in terms of aerosolized drug delivery. The Sidestream/MobilAire system took 1.3–2.0 minutes to deliver an aerosol with a MMAD of 2.1 μm. The Hudson T Up-draft II/Pulmo-Aide system took 8.1–10.3 minutes to deliver aerosolized dornase alfa with MMAD 4.9 μm.

Baseline lung function was better than expected (FVC 99% and FEV_1 88%) in both groups, limiting the potential for improvement. Nevertheless, overall this group of patients improved by 3.4% (CI 3.1, 4.0). There was a trend to greater improvement as measured by FEV_1 with the smaller particle system (2.5% versus 4.3%, $P = 0.06$). Although the baseline lung function of this group was near normal, significant changes resulted following short-term exposure to dornase alfa. This is consistent with the findings of earlier studies. The response in this group of patients with minimal obstruction was greater in those receiving the finer particle aerosol. These findings suggest that with milder disease, possibly as a result of more peripheral drug delivery, the response to dornase alfa can be altered by the choice of nebulizer system. One of the goals of CF treatment is the prevention of irreversible damage to the lungs and airways. Studies show that dornase alfa can be one of the useful tools in our armamentarium to accomplish this goal. It is clear that the choice of aerosol characteristics of dornase alfa and other drugs can have a significant impact on their effectiveness.

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