Current Concepts

Dornase Alfa in Premature Infants With Severe Respiratory Distress and Early Bronchopulmonary Dysplasia

Pamela D. Reiter, PharmD
Susan F. Townsend, MD
Rachelle Velasquez, PharmD

Bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) develop in premature infants as a consequence of respiratory distress syndrome (RDS) and mechanical ventilation. BPD is defined as a requirement for oxygen at 28 days of life with accompanying abnormal respiratory exam and chest radiograph.[1,2] CLD is usually defined as persistence of an oxygen requirement at 36 weeks corrected age (gestational age at birth plus postnatal age),[3] with abnormal respiratory exam and chest radiograph. The major risk factor for both BPD and CLD is the degree of prematurity at birth, with the most premature infants having the greatest risk, affecting up to 70% of infants weighing $\leq$1000 g at birth.[1] The presence of CLD identifies infants at continued risk for respiratory problems during and beyond the first year of life.[1,3,4]

Volutrauma to the premature lung with RDS is considered the primary etiology of BPD.[5] Oxygen toxicity, infection, pulmonary edema from a PDA or excessive fluid administration, increased airway resistance, and lung inflammation are also thought to contribute. Decreased α_1-proteinase inhibitor and vitamin A deficiency have also been implicated as factors.[1] The longer the duration of mechanical ventilation and supplemental oxygen, the more likely is the development of CLD. Damage to the lung produces interstitial edema, atelectasis, inflammation, fibrin deposition, and increased capillary permeability. Inflammation and infection can be accompanied by development of mucous plugging of the airways and recurrent atelectasis.

Treatment modalities to prevent or modify the severity of BPD in premature infants are limited. Exogenous surfactant therapy for RDS results in improved survival and lower acute oxygen and ventilator requirements, but has little impact on the incidence of CLD.[4,6,7] Strategies of mechanical ventilation that minimize potential for lung injury (i.e., lowest peak inspiratory pressures tolerated, high-frequency ventilation, minimizing oxygen toxicity) are recommended. Because of the central role of inflammation in the pathogenesis of BPD, systemic steroids have been used both for treatment and prevention of BPD with mixed results.[8] Novel therapies to reduce lung damage in infants with BPD should be pursued.

Upon the recommendation of our Pediatric Pulmonary Consultant, dornase alfa (Pulmozyme, Genentech) therapy was prescribed for use as a novel treatment in an infant with mucous plugging and BPD. After improvement seen with this initial patient, several more patients were subsequently treated in a similar fashion by a variety of Attending staff. The ensuing data obtained from these patients was obtained through a retrospective chart review. The following cases illustrate the successful short-term use of dornase alfa in seven extremely low birthweight (ELBW) ventilator-dependent infants with evolving BPD, acute pneumonia, and/or mucous plugging. Use of dornase resulted in decreased oxygen requirements and lower requirements for mechanical ventilation. These improvements in pulmonary function may be beneficial in decreasing the extent of further lung injury.

CASE REPORTS

Case 1

A $25^{3/7}$-week male infant of a twin gestation was born at 750 g after uncontrolled preterm labor with cervical dilatation. One- and five-minute Apgar scores were 5 and 7, respectively. Hospital course was complicated by RDS, a PDA ligation, hypotension, pneumothorax requiring insertion of several chest tubes, bilateral grade III intraventricular hemorrhages (IVH), *Escherichia coli* pneumonia and BPD. Despite aggressive treatment of his respiratory deterioration with diuretics, corticosteroids, and inhaled nitric oxide, this infant continued to require substantial support with high-frequency ventilation. Therefore, at six weeks of life, a bronchoscopy was performed and revealed severe mucous plugging. Dornase alfa (2.5 ml) was administered intratracheally and copious secretions were removed with suctioning. Dornase alfa therapy was continued at 2.5 ml every 12 hours for 3 days, followed by 2.5 ml every 24 hours for 3 days. A reduction in concentration of inspired oxygen (Figures 1 and 2), mean airway pressure (Figure 3), and concentration of inhaled nitric oxide (5 to 0 ppm) were observed. Subjective description of the tracheal secretions revealed a substantial

Department of Pharmacy (P.D.R., R.V.), University of Colorado Health Sciences Center, Denver, CO; and Department of Pediatrics (S.F.T.), Section of Neonatology, University of Colorado Health Sciences Center, Denver, CO.

Address correspondence and reprint requests to Pamela D. Reiter, PharmD, Department of Pharmacy, The University of Colorado Health Sciences Center, Campus Box A027, 4200 East Ninth Avenue, Denver, CO 80262.

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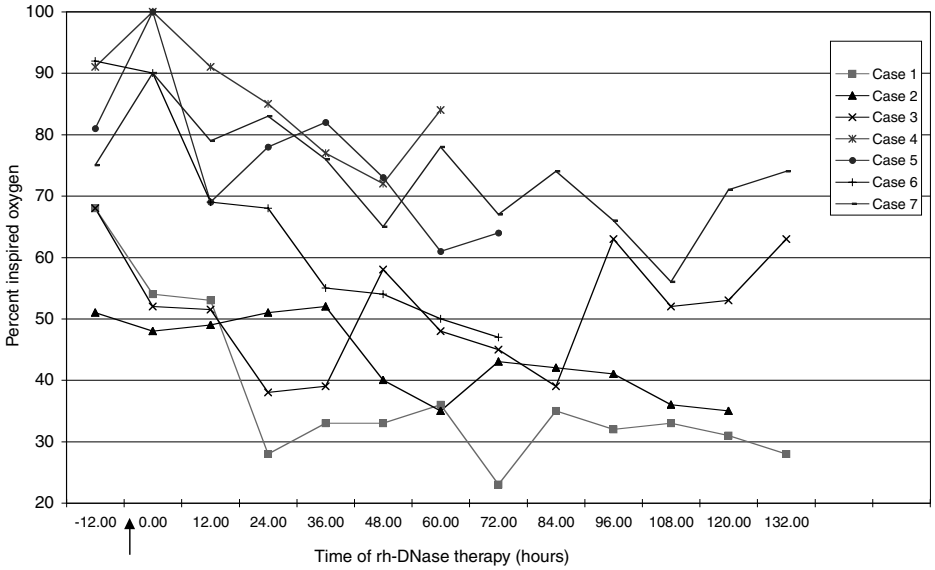

Figure 1. Change in percent inspired oxygen in response to dornase alfa therapy. Arrow indicates onset of therapy.

improvement with dornase alfa therapy from ''thick yellow-white'' secretions to ''clear and thin'' during therapy.

Case 2

A $27^{3/7}$-week female infant was delivered by Cesarean section at 900 g secondary to fetal distress after prolonged rupture of membranes. One- and five-minute Apgar scores were 3 and 8, respectively. Hospitalization was complicated by RDS, PDA ligation, *Stenotrophomonas maltophilia* pneumonia with bacteremia and development of BPD. During the infant's bacterial infection on day-of-life 16, copious thick, yellow respiratory secretions developed and dornase alfa therapy was initiated at 2.5 ml every 12 hours for three days, followed by 2.5 ml every day for 3 days. Dornase alfa therapy was associated with a modest improvement in ventilator requirements (Figure 1) and a subjective improvement in respiratory secretions.

Case 3

A 26-week female infant was delivered vaginally at 890 g secondary to premature prolonged rupture of membranes with evidence of chorioamnionitis. One-, five-, and ten-minute Apgar scores were 1, 7, and 8, respectively. The infant was intubated in

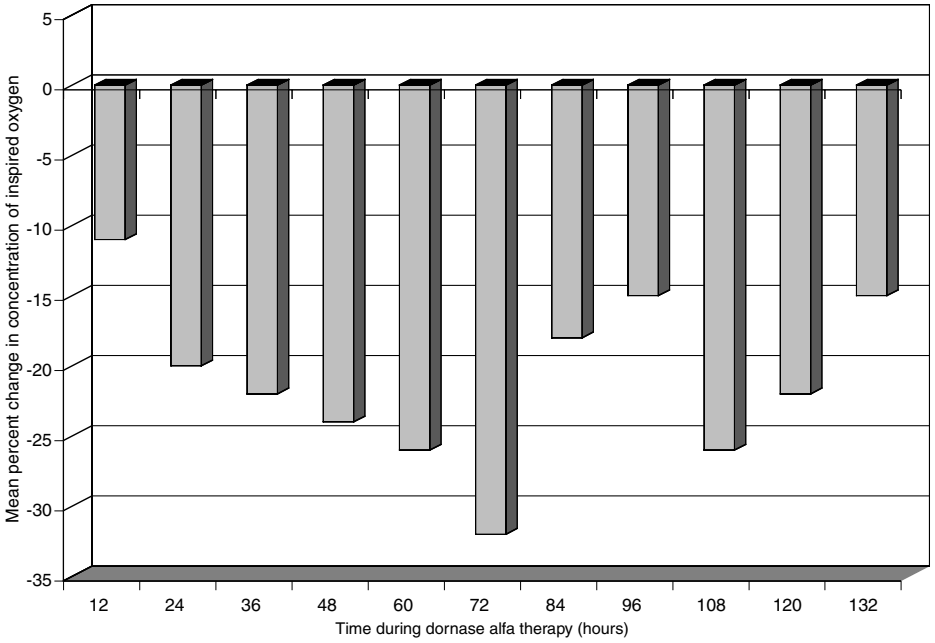

Figure 2. Mean percent change in concentration of inspired oxygen during dornase alfa therapy.

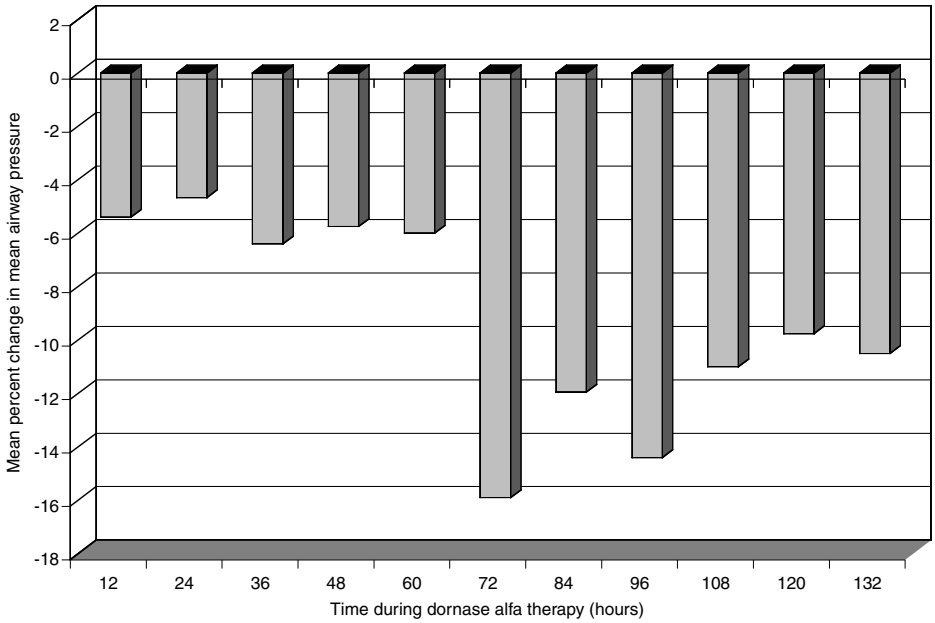

Figure 3. Mean percent change in mean airway pressure during dornase alfa therapy.

the delivery room and received chest compressions and one dose of epinephrine. Hospital course was complicated by RDS, PDA ligation, large pulmonary air leaks requiring multiple chest tubes and BPD. On day-of-life 20, this infant experienced a significant cyanotic spell while on aggressive ventilator support. Pulmonary suctioning revealed a large, thick, yellow mucous plug. Dornase alfa therapy was initiated at 2.5 ml every 12 hours for 3 days followed by 2.5 ml every 24 hours for 3 days. Dornase alfa therapy was associated with a reduction in concentration of inspired oxygen and ventilator requirements (Figures 1–3) with improved clearance of pulmonary secretions. Forty-eight hours after the completion of dornase, this infant deteriorated secondary to complete right-lung atelectasis, presumed secondary to mucous plugging. Therefore, a second 6-day course of dornase alfa was provided, with repeated improvement.

Case 4

A $23^{4/7}$-week female infant was delivered vaginally at 635 g after premature prolonged rupture of membranes, chorioamnionitis, and maternal vaginal bleeding. One-, five-, and ten-minute Apgar scores were 4, 7, and 7, respectively. Hospitalization was complicated by RDS, pulmonary air leaks requiring chest tube insertion, and pneumonia. Thickened pulmonary secretions with mucous plugging, abnormal white blood cell count, worsening chest radiograph, and a positive tracheal aspirate for *S. maltophilia* were noted during the third week of life. Appropriate antibiotics and dornase alfa (2.5 ml every 12 hours for five doses) were initiated. A progressive reduction in concentration of inspired oxygen and mean airway pressure were observed during dornase alfa therapy (Figures 1–3). However, at the completion of dornase alfa therapy, concentration of inspired oxygen promptly escalated back to 90%. There was no significant change noted in the color or viscosity of the pulmonary secretions.

Case 5

A $24^{6/7}$-week male infant was delivered vaginally at 785 g after uncontrolled preterm labor. One-, five-, and ten-minute Apgar scores were 1, 3, and 6, respectively. Hospitalization was complicated by RDS, pulmonary air leaks requiring chest tube insertion, pulmonary interstitial emphysema, and BPD. Thickened pulmonary secretions with mucous plugging, abnormal white blood cell count, significant hypotension, and worsening clinical course were noted during the third week of life. Empiric antibiotic therapy for presumed pneumonia and 3 days of dornase alfa (2.5 ml every 12 hours) were initiated. All cultures (blood, tracheal, urine, and chest tube) remained negative. A reduction in ventilator requirements was associated with dornase (Figures 1–3). Little change was observed in the color or viscosity of pulmonary secretions.

Case 6

A 29-week male infant was delivered by Caesarian section at 1045 g secondary to failure of a cerclage and premature rupture of membrane. One-, five-, and ten-minute Apgar scores were 6, 7, and 9, respectively. Hospitalization was complicated by RDS, PDA ligation, and multiple bacterial pneumonias. His first pneumonia was diagnosed on day-of-life 12 as *S. maltophilia* and was treated with appropriate antibiotics. The infant self-extubated during his antibiotic therapy on day-of-life 19 and did well for 4 days until he experienced a severe respiratory decompensation on day-of-life 23 and required reintubation. Aggressive support was provided with high-frequency ventilation, corticosteroids, bronchodilators, and broadened antibiotics. The infant demonstrated modest respiratory improvement with transition to conventional ventilation. However,

on day-of-life 37 he deteriorated and required high-frequency support again. A tracheal aspirate on the day of deterioration revealed *Enterococcus* species and the infant was started on appropriate antibiotic therapy. A trial of extubation was attempted on day-of-life 42 but resulted in reintubation 2 days later. After this reintubation and observation of thick pulmonary secretions, the infant was started on a 3-day course of dornase alfa. At the time of dornase therapy initiation, the infant required 95% inspired oxygen, which was reduced to 40% at the end of the 3-day treatment (Figure 1). Pulmonary secretions improved markedly from "thick-yellow" to "thin-clear." Successful extubation was achieved on day-of-life 50.

Case 7

A 25-week female infant was delivered by Cesarean section at 715 g secondary to premature prolonged rupture of membranes with evidence of chorioamnionitis. One- and five-minute Apgar scores were 5 and 7, respectively. The hospital course was complicated by RDS, bacterial pneumonia events, and BPD. This infant's first pneumonia was *Klebsiella* on day-of-life 16 and appropriate antibiotic therapy was initiated. A follow-up tracheal aspirate was obtained 5 days later and grew *Enterobacter*. Antibiotic therapy was adjusted to cover both organisms. A decision to begin a 6-day course of dornase alfa was made after copious thick respiratory secretions were noted with increasing ventilator requirements despite antimicrobial and corticosteroid therapy. The infant's ventilator requirements were decreased in association with dornase alfa (Figures 1—3). Within a week of discontinuing antibiotics and dornase alfa therapy, the infant again deteriorated and a new tracheal aspirate grew *S. maltophilia.* Appropriate antimicrobials were initiated and dornase was re-started.

DISCUSSION

These seven cases provide the first description of dornase alfa therapy in ventilated premature infants with early BPD and mucous plugging with or without pneumonia. All of the infants showed some improvement in percent inspired oxygen in relation to treatment (Figure 1). As a group, ventilator requirements (oxygen concentration and mean airway pressure) were reduced at all time points during dornase alfa therapy (Figures 2 and 3). There also appeared to be improvement in the character of their pulmonary secretions. Although the degree of improvement was variable, no infant deteriorated during treatment, and there were no complications related to therapy.

Although clinical improvement was attributed to treatment with dornase alfa, because this was an observational study, it is possible that improvement may have occurred as the natural history of the disease or solely as a result of antibiotic therapy. We believe this is unlikely, as two of the infants (case 3 and 4) deteriorated after dornase therapy was stopped and one case (case 3) was treated with dornase alfa unrelated to antibiotic requirement. In addition, the time course of improvement was similar among all the infants. Thus it appears reasonable to attribute some of the reduction in need for mechanical ventilation and oxygen requirement to treatment with dornase alfa in these infants.

At present, dornase alfa is indicated only for the management of purulent hyperviscous sputum in patients with cystic fibrosis (CF). Approval of this therapy was granted in December of 1993 after clinical trials established efficacy in children and adults with CF and mild-to-moderate lung disease. These trials demonstrated improvement in pulmonary function tests [9–11] reduction in DNA chain length in sputum samples, reduction in dyspnea,[12] reduction in severity of cough and congestion, improvement in quality-of-life, and reduction in risk of pulmonary exacerbation.[13] The utility of dornase alfa in the management of advanced lung disease has met with mixed results, with no improvement noted in one trial ($n=70$) [14] and significant improvement noted in a second trial ($n=320$).[15] Only one case report has been published describing the effect of dornase alfa in a mechanically ventilated infant with CF.[16] No report describes its use in ELBW infants with pneumonia and/or BPD.

Dornase alfa targets infected hyperviscous sputum and destabilizes the thick secretions creating a more liquid specimen that is easily cleared from the pulmonary system. The mechanism behind the destabilization process relies on the fact that bacteria found in sputum of CF patients contain large amounts of extracellular DNA. This DNA is a defense mechanism of the bacteria that inhibits proteolytic enzymes and reduces the efficacy of antimicrobial agents. Dornase alfa cleaves the bacterial DNA into smaller fragments by depolymerisation of the strands thus reducing the adhesiveness of the sputum and enhancing sputum clearance. The effect is negligible on uninfected sputum.

The role of mucolytic therapy in other pulmonary conditions characterized by viscous pulmonary secretions has been examined. Nebulized mesna (sodium salt of 2-mercaptoethane sulfonic acid) failed to improve lung function in two trials involving mechanically ventilated adults.[17,18] In fact, the instillation of mesna caused a rise in airway resistance secondary to bronchospasm. Likewise, *N*-acetylcysteine delivered intratracheally to 10 mechanically ventilated infants (gestational age = 27 ± 1 week; postnatal age = 22 ± 6 days) with BPD, led to an increase in airway resistance and the number of cyanotic spells without an appreciable effect on mucous viscosity.[19] In contrast, the combination of bronchoscopy plus *N*-acetylcysteine in a patient with severe asthma resulted in effective airway clearance and reduced airflow obstruction.[20] Both *N*-acetylcysteine and 2-mercaptoethane sulfonic acid work by breaking covalent bonds of the mucous through opening the disulfide connections. Because bronchospasm is a known adverse effect of many nebulized mucolytics, a combination of a mucolytic with an aerosolized bronchodilator has been advocated.[18,21] Dornase alfa, in contrast to other mucolytics does not provoke a bronchoconstrictive response after administration, making its use in infants with BPD appealing.

A hallmark component of BPD is chronic inflammation and structural changes in the pulmonary parenchyma in response to prolonged mechanical ventilation. Development of mucous plugs

within these inflamed airways can then result in airflow limitations, recurrent atelectasis and worsening lung disease. Additionally, bacterial colonization of endotracheal tubes is common, develops rapidly, and is associated with the severity of BPD.[22–24] It seems reasonable to hypothesize that a drug with properties to facilitate airway mucous clearing, without causing post-administration bronchospasm, would be clinically important in infants with colonized or infected endotracheal tubes.

This report describes the clinical improvement in airway clearance and ventilator requirements, without evidence of side effects, in seven ventilator dependent premature infants with evidence of pneumonia or mucous plugging and developing or established BPD. This represents a first step to additional research to determine the best clinical role for this mucolytic. Future studies to examine the role of dornase alfa in this patient population including sputum viscosity analysis, pulmonary function testing and sputum protein analysis are needed to establish patient selection and optimal duration of and response to therapy. Ultimately, patient outcomes such as time on mechanical ventilation, cost of care and long-term pulmonary status should be measured.

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