Angioedema Associated With Nebulized Recombinant Human DNase in a Preterm Infant: Case Report

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Pulmonary atelectasis leads to difficulties in weaning of the neonates from mechanical ventilation. The management of persistent atelectasis in neonates constitutes a common challenge for physicians. Several reports suggested Recombinant human DNase (rhDNase) as a beneficial therapy for neonates with persistent atelectasis by reducing mucous viscosity. No adverse effect associated with rhDNase treatment was reported in neonates. Herein, we report probable adverse reactions associated with rhDNase use in a preterm infant. Therefore, we suggest that clinicians must be aware of this reaction in neonates and should carefully follow up these infants for the development of adverse reactions. We think that more clinical experience and data are needed to define its tolerability and adverse effect profile in neonates.

ABBREVIATIONS CF, cystic fibrosis; CPAP, continuous positive airway pressure; PA, pulmonary atelectasis; RhDNase, recombinant human DNase

KEYWORDS angioedema; preterm infant; recombinant human RhDNase

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Introduction

Atelectasis can be defined as a collapse or loss of lung volume. It is common in newborns with severe respiratory infections and often requires invasive ventilation.¹ Pulmonary atelectasis (PA) may be a frequent complication of parenchymal lung diseases, such as pneumonia, or may occur secondary to surfactant deficiency in preterm infants. It may also develop as a consequence of airway obstruction associated with mucus accumulation or misplacement of the endotracheal tube. Therefore, neonatal PA may be associated with difficulties in weaning infants from mechanical ventilation.² Management of persistent atelectasis in neonates remains a common challenge. Recombinant human DNase (rhDNase) is an enzyme that breaks down DNA strands in airway secretions, hydrolyzes the DNA in the mucus and/or sputum, reduces viscosity in the lungs, promotes secretion clearance, and allows for improved airflow. Therefore, it has been suggested to be used in the treatment of infants with cystic fibrosis (CF) and persistent atelectasis.^{3,4} Also, rhDNase is used in infants with respiratory syncytial virus bronchiolitis and for atelectasis of presumably infectious origin in non-CF patients.⁵ Recombinant human DNase has been reported to be well tolerated in children with CF, adults, and newborns.^{5,6} Adverse events related to rhDNase therapy include voice alteration, laryngitis, pharyngitis, rash, chest pain, dyspnea, dyspepsia, and urticaria.⁶

Angioedema has been defined as the swelling of deep subcutaneous areas in the skin or mucous membranes. It can be triggered by several foods and

medications associated with angioedema and urticaria. Non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors were reported as the most common medications.⁷ We report a preterm infant who developed angioedema following rhDNase treatment for persistent atelectasis. To the best of our knowledge, angioedema associated with rhDNase use in newborns or in any other age groups of patients has not been reported.

Case Report

A premature infant was born with a birth weight of 830 g at 25 weeks gestational age. She was admitted to the neonatal intensive care unit because of prematurity and respiratory distress syndrome. She was intubated in the delivery room, given 1 dosage of surfactant (poractant alfa), and remained ventilated for 4 days. She required reintubation because of acute deterioration associated with neonatal sepsis on day 11. *Candida albicans* was isolated on both tracheal aspirate and blood cultures. Therefore, amphotericin B was started according to culture sensitivities. She was re-extubated to nasal continuous positive airway pressure (CPAP) via ventilator on day 14 of life. However, the ventilator parameters and FiO₂ requirements increased during follow-up. She was reintubated on day 22. Because the chest radiograph showed right-sided collapse, she was nursed right side up, and chest physiotherapy was performed. However, she did not respond to conventional methods, such as position change, chest physiotherapy, routine oropharyngeal aspirations,

Figure. Apparent swelling of the eyelids after 2 hours of recombinant human DNase.

and *N*-acetylcysteine treatment to release the mucus plug. Several extubation attempts were unsuccessful because of persistent atelectasis, but she was eventually extubated to CPAP on day 45. Because there was no response to *N*-acetylcysteine, it was stopped on day 48. As FiO_2 increased to 50% to 60% and positive end expiratory pressure of 7 to 8 cm H_2O in nasal CPAP, she was given rhDNase via nebulizer mask at a dose of 1.25 mg by the nurse on day 51 of life. The second dose was administered 12 hours after the first dose by the same nurse. No other inhaler therapy was used at this time. During this treatment, at both doses, the eyes of the patient were covered to prevent any ocular damage.

Two hours after the second dose of rhDNase, swelling of the eyelids was observed (Figure). The patient could not tolerate any further doses because of the adverse effect. It was an isolated reaction without urticaria or rash. No difficulty in swallowing and/or respiration was determined. The infant's vital signs were within normal ranges, including a respiratory rate of 44/min, pulse rate 128/min, blood pressure 82/48 mm Hg, and SpO_2 93%. Nasal CPAP parameters improved with

an FiO_2 requirement of 21% to 30% and positive end expiratory pressure of 5 to 6 cm H_2O after 2 doses of rhDNase treatment. The infant did not take any other medication 6 hours before and after rhDNase therapy. Table 1 shows the timeline of all of the drugs administered to the patient during the day of angioedema. The patient was given intravenous diphenhydramine 1 mg/kg just after the notification of angioedema, and the swelling resolved within 24 hours. No other drugs were administered during this period. No other complications and no progression to anaphylactic shock were observed. There was no similar allergic reaction to any drug during hospitalization or family history in the past.

Discussion

Pulmonary collapse and atelectasis may occur secondary to mucus plug in neonates. In addition to conventional methods, rhDNase therapy was suggested to be used in newborns with persistent PA by decreasing mucous viscosity and improving oxygenation.⁵ To date, no adverse effect associated with rhDNase treatment has been reported in neonates. To the best of our knowledge, this is the first report of severe angioedema associated with the use of nebulized recombinant human DNase in a preterm infant, as well as in children with CF and adults.⁶

At present, no evidence-based medical treatment for persistent atelectasis in newborn exists. The inflammatory response in the airway leads to necrosis in respiratory epithelium, tissue edema, and increased mucus production, resulting in the formation of thick mucus plugs in the airway lumen and atelectasis.⁸ Pulmonary secretions attain their viscosity from the presence of extracellular DNA from degenerating polymorphonuclear lymphocytes. Recombinant human DNase reduces sputum viscosity by hydrolyzing extracellular DNA, thus transforming it as a flowing liquid that facilitates the clearance.⁹ The use of nebulized RhDNase has been established as an effective therapy for the liquefaction of viscous mucus in CF and other respiratory diseases, such as respiratory syncytial virus bronchiolitis and asthma.^{4,9}

There are limited data for the use of rhDNase in neonates. El Hassan et al⁴ reported the use of nebulized rhDNase in 3 preterm neonates with atelectasis. Erdevi et al⁵ administered nebulized rhDNase in 12 newborns, 10 of whom were preterm. The demographic data of patients were similar to those of our patient. All patients had underlying lung disease and radiologi-

Table 1. The Dose Administration Time of All Drugs Administered to the Patient During the Day of Angioedema

Inhalation Drug	Dose and Dosing Interval	Time of Administration	
Dornase alfa solution	1.25 mg every 2 hr	12:30	24:30
Salbutamol solution	0.2 mg/kg every 2 hr	06:00	18:00
Budesonide solution	125 mcg per dose every 2 hr	06:30	18:30

Table 2. Naranjo Scale for Our Patient

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	1	0	0	1
4. Did the adverse reaction reappear when the drug was readministered?	2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	2	0	2
6. Did the reaction reappear when a placebo was given?	-1	1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	1	0	0	0
Total score				5

cally documented atelectasis that was unresponsive to conventional methods, such as position change, chest physiotherapy, endotracheal suctioning, and N-acetylcysteine treatment to release the mucus plug. The rescue use of nebulized rhDNase in these cases was successful, with a rapid improvement in clinical and radiologic parameters, and no adverse effects were reported.^{4,5} Our patient had viscous secretions that led to atelectasis. Because it did not respond to conventional treatment, we used nebulized rhDNase as rescue treatment. Based on the previous reports we administered a nebulized dose of 1.25 mg of rhDNase twice daily at intervals of 12 hours.¹⁰

Angioedema is an abrupt swelling of the skin and/or mucous membranes of the upper respiratory or gastrointestinal tract.¹¹ The swelling is often skin-colored, or slightly erythematous and painless. Angioedema is a consequence of increased vasodilation and capillary permeability leading to plasma extravasation in response to mediators, such as histamine and bradykinin.¹² A precipitant (e.g., food, drugs, physical stimuli) can cause immunoglobulin E-mediated or non-immunoglobulin E-mediated allergic reactions. Drug-induced angioedema without urticaria may be caused by an immunoglobulin E-mediated allergic reaction. However, the pathogenesis remains unclear in most of these reactions. Antihistamines are often used in treatment.¹³ The reaction generally occurs within 2 hours of exposure to the responsible allergen.¹³ Consistent with the literature, our patient developed swelling of the eyelids 2 hours after the second dose of nebulized

rhDNase. This reaction was isolated because the patient had no findings of systemic anaphylaxis. There was no difficulty in swallowing or respiration. Her pulse rate, blood pressure, and respiratory rate were within normal limits. In accordance with the literature, swelling resolved within 24 hours. A diagnosis of drug-induced angioedema without urticaria was suggested with these clinical findings. Naranjo scale has been generally used to classify adverse drug reaction as doubtful (0 points), possible (1–4 points), probable (5–8 points), and definite (≥ 9 points).¹⁴ We employed Naranjo scale to define the temporal relationship and the biologic/pharmacologic plausibility between the rhDNase exposure and angioedema. According to the score in our patient, this reaction could be defined as a probable adverse drug reaction (Table 2). The treatment is usually supportive. Corticosteroids and antihistamines are the treatment of choice, but there is no proven therapeutic agent. Only epinephrine is useful in allergic angioedema and anaphylaxis.¹³

Nebulized rhDNase treatment has generally been well tolerated in clinical trials. No adverse effect of rhDNase treatment in a series of 22 preterm and term neonates with persistent atelectasis was observed in a recent study.¹⁵ In addition, angioedema has not been shown as a side effect of rhDNase treatment in both the pediatric and the adult literature. In the presence of all data, our patient seems to be the first to develop angioedema after this treatment. Therefore, we suggest that rhDNase may lead to a serious adverse effect leading to the cessation of treatment in a preterm infant. This

adverse effect should be considered by both physicians and neonatal nurses during administration in neonates.

Herein, we reported angioedema as a rare adverse effect of rhDNase in a preterm infant with persistent atelectasis. Because this is a very rare adverse effect, we may suggest vigilant monitoring during administration of rhDNase, especially in preterm neonates. Because we have limited data about the short- and long-term effects of rhDNase treatment in neonates, more clinical experience is required to define its tolerability and adverse effect profile in this high-risk population.

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