DNase Treatment in Primary Ciliary Dyskinesia—Assessment by Nocturnal Pulse Oximetry

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Key words: DNase; primary ciliary dyskinesia; pulse oximetry; body plethysmography.

INTRODUCTION

DNA from disintegrating neutrophils is thought to be an important determinant of the high viscosity of cystic fibrosis sputum. Recombinant human deoxyribonuclease (DNase), an enzyme which cleaves DNA, has proven to be effective in improving sputum clearance from the airways of patients with cystic fibrosis (CF). Inhaled DNase improves pulmonary function, reduces the frequency of respiratory tract infections and improves general well-being in CF.

Primary ciliary dyskinesia (PCD), like CF, is a chronic lung disease in which sputum retention leads to lung damage. Impairment of mucociliary transport results in chronic sinusitis, chronic bronchitis, and subsequently bronchiectasis, and in about 50% to situs inversus. Currently, PCD patients are treated with chest physiotherapy, antibiotics, and bronchodilators. We present here an infant with PCD. His severe respiratory symptoms and hypoxemia did not improve, despite nebulized isotonic NaCl solution, physiotherapy, and aggressive antibiotic treatment. Immediately after starting nebulized DNase therapy the respiratory symptoms, lung function, and overnight oximetry improved. During two readmissions because of acute worsening of dyspnea, the baby again showed overnight improvements on treatment with DNase, antibiotics, and bronchodilators. Withholding DNase during an asymptomatic period caused no worsening. The therapeutic potential of nebulized DNase in PCD should be established by controlled trials.

CASE REPORT

The patient presented prenatally because routine ultrasound examination during pregnancy had shown situs inversus totalis. An older sister had PCD, proven by ciliary motility studies of a nasal mucosal biopsy and electron microscopy of a bronchial mucosal biopsy. The boy was born at term with Apagar scores after 1, 5, and 10 min of 8, 7, and 9, respectively. Because of neonatal respiratory insufficiency, perhaps due to aspiration of amniotic fluid, the patient was intubated and mechanically ventilated for 1 day with maximal pressures up to 28 cm H2O, maximal FiO2 of 1.0 and treated with intravenous antibiotics for 7 days (amoxicillin and cefotaxime). Chest X-ray showed partial atelectasis of the right upper and lower lobes, as well as bilaterally increased bronchial markings. After extubation he continued to be tachypneic (respiratory rate 65–82/min), despite physiotherapy, nebulized isotonic NaCl solution, bronchodilators, and oral antibiotic treatment with amoxycillin. Because of persisting hypoxemia, he required supplemental oxygen (FiO2 of 0.25). Sputum cultures revealed E. coli. On auscultation, wheezes and crackles were heard over both lungs. On days 22 and 31 of life, overnight hemoglobin oxygen saturation measurements without supplemented oxygen were recorded (Nellcor oximeter, N-200, Hayward, CA, USA). Saturations were below 95% during 84% of total recorded time (10.44 hr) on day 22, and during 89% of recorded time (11.55 hr) on day 31 (Fig. 1). On day 34 treatment with nebulized recombinant DNase (Pulmozyme®, Roche) was started (2.5 mg once
daily via a Pulmo Aid compressor (DeVilbiss Health Care, Heston Middlesex, U.K.) and a sidestream nebulizer (Medic Aid, West Sussex, U.K.). Within 2 days his dyspnea subsided and his respiratory rate dropped to 40–60/min. On physical examination, there was marked lessening in retractions and normalization of breath sounds. After 4 days of DNase treatment, the overnight saturation measurements were repeated. The saturation was below 95% for 47% and between 95–100% for 53% of the total recorded time (11.30/hr) (Fig. 1). On days 32 and 45, before and during DNase treatment, body plethysmography (modified Baby Bodybox, Jaeger, Würzburg, Germany) was performed under sedation with triclofos sodium 75 mg/kg. The thoracic gas volume (TGV) was elevated on day 32 (38 mL/kg) and had decreased to 31 mL/kg on day 45 (normal mean value approximately 25 mL/kg; in newborns up to 30 mL/kg). The mean tidal volume calculated from a series of 20 breaths increased from 7.6 mL/kg to 8.3 mL/kg. He was discharged from the hospital on day 41 with continuation of DNase (2.5 mg once daily) and daily prophylactic antibiotic treatment with amoxycillin/clavulanic acid. On follow-up 3 weeks later, improvement was maintained and physical examination showed quiet breathing without retractions and some crackles. His weight gain was normal. During the following 7 months, two readmissions were necessary because of acute worsening of dyspnea and cough. At the time of both admissions it appeared that the parents had discontinued nebulized medication, including DNase, for some time. Overnight improvement was seen both times after starting i.v antibiotics, nebulized bronchodilators, and DNase. During the second readmission, when the patient was 7 months old, we decided to discontinue DNase treatment when the patient was in an optimal condition. Clinical observation and overnight oximetry before and 3 days after stopping DNase showed no worsening. Therefore, we decided to stop DNase treatment. No further exacerbations of lung infection have occurred to this day.

DISCUSSION

This is, as far as we know, the first report on the therapeutic use of inhaled DNase in an infant with severe chronic respiratory symptoms due to PCD. Initially, we documented rapid improvement of oxygenation, lung function, and symptoms shortly after starting DNase when treatment with antibiotics and physiotherapy had proven unsuccessful. Two more acute episodes also showed rapid clearing of symptoms with DNase, although simultaneous treatment with antibiotics made it difficult to estimate the contribution of DNase to the child’s improvement.

There is one previous report of an older patient with PCD whose pulmonary function and gastrointestinal symptoms rapidly improved after DNase. DNase has mainly been studied in CF patients, but has also been used to treat other lung diseases. Two reports describe the benefits from rhDNase in asthmatic children with atelectasis and mucus plugging. The DNA level of sputum of asthmatics has been observed to be 3 times higher compared with healthy controls. Although there are no data on DNA content of airway mucus in PCD, Potter et al. describe that the amount of DNA in non-CF bronchiectasis is one-quarter that found in CF patients, which is still elevated compared to healthy controls. Hydrolizing sputum DNA in PCD might transform a non-flowing viscous gel into a less viscous gel, but it is difficult to see how this could lead to better expectoration. Sputum clearance in PCD patients largely depends on effective cough, and this requires high flows, low sputum tenacity and interfacial tension, and preserved sputum viscosity. Hence, reducing viscosity by means of DNase should reduce rather than improve cough clearing. Therefore, other mechanisms may explain our observations. A hypothetical possibility is that lysing airway secretions increases antibiotic penetration and bacterial kill in the airways, thereby improving lung function and clinical condition.

Of the outcome measures we studied, measurements of overnight saturation seemed especially valuable for objectively assessing the effect of treatment. We also documented that, after initiation of DNase, TGV and breathing frequency decreased and tidal volume increased. This

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suggests lessening of hyperinflation, increased compliance, and less small airway obstruction. During the two readmissions, striking improvements were seen within 1 day of starting DNase and antibiotics. We speculate that adding DNase was responsible for this unusually rapid improvement. Once the acute problems due to sputum retention were solved, withholding DNase did not cause any deterioration. Until a beneficial effect of DNase on acute obstructive airway disease due to PCD in infancy has been validated in a controlled study, a trial of inhaled DNase in acutely dyspneic PCD infants should be considered.

REFERENCES