Pharmacotherapy of Impaired Mucociliary Clearance in Non-CF Pediatric Lung Disease. A Review of the Literature

Ruben Boogaard, MD,1* Johan C. de Jongste, MD, PhD,1 and Peter J.F.M. Merkus, MD, PhD1,2

Summary. Mucoactive agents are used to treat a variety of lung diseases involving impaired mucociliary clearance or mucus hypersecretion. The mucoactive agents studied most frequently are N-acetylcysteine (NAC), recombinant human DNase (rhDNase), and hypertonic saline. Studies on the efficacy of these have been mainly conducted in adults, and in patients with cystic fibrosis (CF). The exact role of mucoactive agents in children with non-CF lung disease is not well established. We present an overview of the current literature reporting clinical outcome measures of treatment with NAC, rhDNase, and hypertonic saline in children. Pediatr Pulmonol. 2007; 42:989–1001. © 2007 Wiley-Liss, Inc.

Key words: mucolytic; sulfhydryl compounds; N-acetylcysteine; dornase alfa; hypertonic saline; respiratory tract disease.

INTRODUCTION

Mucus clearance is an important primary innate airway defense mechanism, and our understanding of the key parameters underlying its function has grown rapidly in the last decade.1,2 Impaired mucus clearance or mucus hypersecretion are important clinical features in diseases such as cystic fibrosis (CF), recurrent bronchitis, asthma, and primary ciliary dyskinesia (PCD). Moreover, viral respiratory tract infections—that occur frequently during childhood—may cause epithelial damage and loss of cilia,3 and thus impaired mucus clearance through secondary ciliary dysfunction. Impaired clearance causes mucus to accumulate in the airways and to initiate cough and sputum production. Accumulated mucus can lead to airways obstruction, bacterial colonization, and recurrent infections, negatively affecting quality of life. By completely obstructing the peripheral airways it may lead to atelectasis and hypoxia, and may contribute to a fatal outcome, such as in an acute asthma exacerbation.4

Mucoactive agents are drugs that are meant to change the properties of airway secretions.5 Many different mucoactive agents have been evaluated for their ability to either change the properties of airway mucus, or to decrease mucus secretion.6,7 Classified by proposed mechanism of action, they encompass classical mucolytics, peptide mucolytics, nondestructive mucolytics, expectorants, mucokinetic agents, and mucoregulators (Table 1).

One possible means to evaluate a mucoactive agent is to assess its effect on mucociliary clearance (MCC) or cough clearance with the use of radiolabeled aerosol. Discussing this subject is outside the scope of this review. Moreover, studies on mucoactive agents in CF patients, and studies on physiotherapy or secretion clearance techniques in (pediatric) lung disease patients have been reviewed by others, and will therefore not be discussed in this review. The interested reader is referred to existing reviews that cover:

• basic and clinical aspects of mucociliary clearance;8
• regulation of mucociliary clearance in health and disease.9

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The aim of the present review is to summarize the published literature on the mucoactive agents most frequently used and studied in children with non-CF lung disease, that is, NAC and other sulfhydryl compounds, rhDNase, and hypertonic saline. We will focus on literature reporting effects of mucoactive agents on clinical outcome measures, such as length of hospital stay, symptom severity, and chest radiographs.

METHODS

We searched MEDLINE (1966 to June 2007) with the medical subject headings (MESH): ‘respiratory tract diseases,’ ‘acetylcysteine,’ ‘sulphhydryl compounds,’ ‘hypertonic saline solution,’ and ‘DNASE1 protein, human’—the latter is the MESH term for the drug ‘recombinant human DNase (rhDNase, dornase alfa)’. Randomized controlled trials (RCTs) as well as uncontrolled, observational studies retrieved by MEDLINE, published in English and reporting clinical data on children aged 0–18 years were looked up and their reference lists were scanned for relevant unretrieved material. The Cochrane library was checked for any additional clinical trials.

RESULTS OF LITERATURE SEARCH

A total of 34 relevant articles were retrieved (Fig. 1). Twelve articles reported RCTs, while 22 articles reported uncontrolled clinical observations.

N-ACETYLCYSTEINE AND OTHER SULFYHYDRYL COMPOUNDS

Mode of Action

N-acetylcysteine (NAC) and the other sulphhydryl compounds—that is, S-carboxymethylcysteine (carboxycysteine) and 2-mercaptoethane sulfonate (Mesna)—depolymerize mucus in vitro by breaking disulfide bonds of the glycoproteins, thereby lowering viscosity and potentially improving expectoration.21 Besides potential effects on MCC, sulphhydryl compounds have anti-oxidant effects that could be useful in preventing lung damage in...
chronic lung disease. NAC is usually given orally, as inhalation can cause bronchospasm in patients with airway hyperresponsiveness,\textsuperscript{22,23} releases an unpleasant sulfurous smell and is time consuming. However, for orally administered NAC to exert a clinical effect—that is, by changing the properties of mucus—it must pass into the mucus. There is no proof that orally administered NAC results in therapeutic concentrations in airway secretions.\textsuperscript{24} In some studies in healthy adults or in chronic bronchitis patients, sulfhydryl compounds improved MCC, whereas in other such studies there was no effect.\textsuperscript{13}

Randomized Controlled Trials of NAC in Non-CF Lung Diseases

Most studies indicating efficacy of oral NAC or carbocysteine concern adults with chronic bronchitis or chronic obstructive pulmonary disease (COPD). A Cochrane review showed slightly fewer exacerbations and slightly shorter period of disability, but no difference in lung function, in patients using these agents.\textsuperscript{25} These benefits of oral NAC might be due to its antioxidant properties rather than its mucolytic properties. Sulfhydryl compounds have been studied less intensely in pediatric patients (Table 2).\textsuperscript{14,26–30}

Primary Ciliary Dyskinesia

Stafanger et al.\textsuperscript{26} conducted a double blind, randomized crossover trial in 13 out-clinic patients with PCD. Oral NAC for 3 months had no effect on subjective clinical scores, lung function parameters and ciliary function.

Chronic Lung Disease of Infancy

Bibi et al.\textsuperscript{27} conducted a crossover trial in which they intratracheally administered NAC or placebo for 7 days to premature infants ventilated for chronic lung disease. Airway resistance at day 3 worsened twofold in the NAC group. Dynamic compliance, clinical signs, ventilatory settings and chest X-ray scores did not change. Two patients treated with NAC showed more cyanotic spells and bradycardia. A large RCT (n = 391) aimed to assess possible anti-oxidant benefits of intravenous NAC in premature infants with extremely low birth weight.\textsuperscript{28,29} It appeared that a 6-day course had neither effect on mortality or the incidence of bronchopulmonary dysplasia (BPD), nor on lung function.\textsuperscript{28,29}

Other Diseases

Symptom scores for children admitted with pneumonia or asthma did not differ between groups receiving oral
TABLE 2—Literature on the Clinical Effects of Sulfhydryl Agents in Non-Cystic Fibrosis Pediatric Patients

<table>
<thead>
<tr>
<th>Disease, patient characteristics</th>
<th>Study design</th>
<th>N</th>
<th>Age mean or median (range)</th>
<th>Dose of sulfhydryl agent, mode of administration</th>
<th>Reported results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>RCT, cross-over&lt;sup&gt;20&lt;/sup&gt;</td>
<td>13</td>
<td>29.7 (2–47) years; 6 patients &lt;16 years</td>
<td>200 mg NAC 3 times a day (&lt;30 kg), 400 mg NAC twice daily (&gt;30 kg) for 3 months; oral</td>
<td>No effect on subjective clinical score, lung function, sputum bacteriology, blood leukocyte count, sedimentation rate, anti-microbial antibodies, and ciliary function</td>
</tr>
<tr>
<td>Chronic lung disease in premature infants, during mechanical ventilation</td>
<td>RCT, cross-over&lt;sup&gt;21&lt;/sup&gt;</td>
<td>10</td>
<td>27 (2.5–33) weeks (gestational age); 22 (10–70) days (postnatal age)</td>
<td>0.5 ml NAC 5% every 4 hr for 1 week; endotracheal instillation</td>
<td>Negative effect on total airway resistance; Side effects: bradycardia and cyanotic spells</td>
</tr>
<tr>
<td>Extremely low birth weight infants</td>
<td>RCT&lt;sup&gt;20&lt;/sup&gt;</td>
<td>391</td>
<td>26 weeks (SD: 1.8) (gestational age); 1 day (postnatal age)</td>
<td>16–32 mg/kg/day of NAC for 6 days; intravenously</td>
<td>No effect on chest X-ray score and duration of respiratory support</td>
</tr>
<tr>
<td>Extremely low birth weight infants</td>
<td>RCT&lt;sup&gt;29&lt;/sup&gt;</td>
<td>33</td>
<td>25 (2.4–29) weeks (gestational age); 1 day (postnatal age)</td>
<td>16–32 mg/kg/day of NAC for 6 days; intravenously</td>
<td>No effect on lung function at discharge from NICU (compliance, resistance, FRC, indices of gas mixing)</td>
</tr>
<tr>
<td>Bronchopneumonia or asthma in hospitalized children</td>
<td>“double blind” trial&lt;sup&gt;30&lt;/sup&gt;</td>
<td>47</td>
<td>2 months to 13 years</td>
<td>100 mg NAC 5 times a day; oral</td>
<td>No effect on cough, dyspnea, auscultation, and chest X-ray</td>
</tr>
<tr>
<td>Severe recurrent atelectasis in premature infants during mechanical ventilation</td>
<td>CS&lt;sup&gt;31&lt;/sup&gt;</td>
<td>5</td>
<td>23–34 weeks (gestational age); 3–26 weeks (postnatal age)</td>
<td>2 ml NAC 5% 4 times a day for 2–4 days; nebulization</td>
<td>Improved chest X-ray, and ventilator settings</td>
</tr>
<tr>
<td>Acute atelectasis following smoke inhalation in mechanically ventilated child</td>
<td>CS&lt;sup&gt;32&lt;/sup&gt;</td>
<td>1</td>
<td>12.5 years</td>
<td>2 ml NAC 20% every 2 hr on 1st day, 4 times a day on 2nd to 5th day; nebulization</td>
<td>Improved chest X-ray, sputum volume, and cough</td>
</tr>
<tr>
<td>Status asthmaticus</td>
<td>CS&lt;sup&gt;33&lt;/sup&gt;</td>
<td>14</td>
<td>5.5 (1.5–19) years</td>
<td>1 ml/kg bodyweight of 4% Mesna solution; bronchoalveolar lavage</td>
<td>Improved blood gases, chest X-ray</td>
</tr>
<tr>
<td>Inhalation injury in mechanically ventilated children</td>
<td>historic control group&lt;sup&gt;34&lt;/sup&gt;</td>
<td>90</td>
<td>7.7 years (SD: 5)</td>
<td>3 ml NAC 20%, alternated with 5000 units heparin, every 4 hr for 7 days; nebulization 20–30 mg/kg/day of NAC for 5–10 days; intra-muscular</td>
<td>Improved reintubation rate, mortality, and atelectasis</td>
</tr>
<tr>
<td>Lower respiratory tract infection in hospitalized children</td>
<td>CS&lt;sup&gt;35&lt;/sup&gt;</td>
<td>103</td>
<td>2 months to 11 years</td>
<td>3 ml NAC 20%, alternated with 5000 units heparin, every 4 hr for 7 days; nebulization 20–30 mg/kg/day of NAC for 5–10 days; intra-muscular</td>
<td>Improved symptoms, chest X-ray, and sputum culture</td>
</tr>
<tr>
<td>Obstructive respiratory disease (atelectasis; bronchiectasis)</td>
<td>CS&lt;sup&gt;36&lt;/sup&gt;</td>
<td>67</td>
<td>2.9 years (23 days to 11 years)</td>
<td>10–50 mg/kg/day of NAC for 7–110 days; oral</td>
<td>Improved chest X-ray, and ‘clinical results’</td>
</tr>
<tr>
<td>Acute (recurrent) bronchitis</td>
<td>CS&lt;sup&gt;37&lt;/sup&gt;</td>
<td>20</td>
<td>3–14 years</td>
<td>100–200 mg NAC 3 times a day for 4 days; oral</td>
<td>Improved duration of cough, and lung function</td>
</tr>
<tr>
<td>Chronic lung diseases</td>
<td>CS&lt;sup&gt;38&lt;/sup&gt;</td>
<td>52</td>
<td>2 months to 12 years</td>
<td>200–600 mg/day of NAC for 4 weeks; oral</td>
<td>Improved auscultation. Doubtful effect on chest X-ray No effect on lung function, and regional ventilation-perfusion</td>
</tr>
</tbody>
</table>

N, number of patients; RCT, randomized controlled trial; CS, case series or case report; NAC, N-acetylcysteine; Mesna, 2-mercaptoethane sulfonate; PEFR, peak expiratory flow rate; RV/TLC, residual volume to total lung capacity; FVC, forced vital capacity; \(V_{50\%VC}\), maximum flow at 50% of vital capacity; FRC, functional residual capacity; NICU, neonatal intensive care unit.
NAC or placebo.\textsuperscript{30} This small study was described as “double blind,” but seems of poor methodological quality as randomization and treatment allocation remain unexplained and the study population was very heterogeneous.

**Observational Studies of NAC in Non-CF Lung Diseases**

Several uncontrolled observations report beneficial effects of nebulized NAC in children with atelectasis, (acute) asthma, inhalation injury, and lower respiratory tract infections, but RCTs in these patient groups are lacking (Table 2).

**Atelectasis**

Amir et al.\textsuperscript{31} reported a possible beneficial effect of nebulized NAC on chest X-ray appearance and ventilatory settings in five mechanically ventilated premature infants with severe recurrent atelectasis. Wiener et al.\textsuperscript{32} administered nebulized acetylcysteine to a mechanically ventilated child with atelectasis caused by smoke inhalation. That done, sputum volume increased and the atelectasis cleared within 2 days.

**Asthma**

By liquefying mucous plugs, mucolytics could have potential benefit in acute asthma. On the other hand, NAC may cause bronchoconstriction when children have Airways hyperresponsiveness.\textsuperscript{22,23} Pretreatment with bronchodilators could prevent this. Uncontrolled observations in adults with acute severe asthma, unresponsive to regular therapy, nevertheless showed beneficial clinical effects of nebulized or bronchoscopically instilled NAC.\textsuperscript{33,34} Kyncl et al.\textsuperscript{35} reported improved blood gas values and chest X-ray pictures after bronchial lavage with Mesna in 14 children with status asthmaticus. However, RCTs are lacking and so are studies on NAC in stable asthmatic children.

**Inhalation Injury**

Desai et al.\textsuperscript{36} studied the combined, potential mucolytic and anti-oxidant properties of NAC in children mechanically ventilated for inhalation injury. The results were suggestive of a benefit, as inhalation of alternating NAC and heparin decreased mortality, reintubation rate and incidence of atelectasis. Nevertheless, as the control group was a historical one, these results have to be interpreted with caution.

**Lower Respiratory Tract Infection**

Several uncontrolled studies claim clinical benefits of NAC in children with lower respiratory tract infections or chronic lung diseases.\textsuperscript{37–40} For one, Santangelo et al.\textsuperscript{37} do so for combined treatment of cefuroxime and intra-muscular NAC in children with lower respiratory tract infections. Another study also reported good “clinical and radiological results” of oral NAC in children with different lower respiratory tract diseases, such as atelectasis, “bronchiolopathy,” or bronchiectasis.\textsuperscript{38} Two patients with atelectasis and “bronchiolopathy”, however, showed “asphyxia.” The authors suggest this might have been due to excessively rapid liquefaction of retained secretions. Nevertheless, this explanation seems unlikely as there is no proof that orally administered NAC reaches therapeutic concentrations in airway secretions.\textsuperscript{24} Nikolic and Korac\textsuperscript{39} reported that oral NAC improved symptoms and lung function in children with recurrent bronchitis. Rudnik et al.\textsuperscript{40} studied children with “chronic lung diseases” and reported clinical and radiological improvement after oral NAC treatment. There was no effect, however, on lung function and regional ventilation and perfusion.

As none of these studies included control groups, it is impossible to conclude whether NAC indeed contributed to the reported improvements.

**RECOMBINANT HUMAN DNASE (RHDNASE)**

**Mode of Action**

Purulent sputum from patients with CF and several other respiratory diseases contains high concentrations of DNA released from degenerating polymorphonuclear leucocytes.\textsuperscript{41,42} Higher DNA content in CF mucus is associated with higher mucus viscosity and mucus elastic modulus,\textsuperscript{43} and adding exogenous DNA to sputum increases both viscosity and elasticity.\textsuperscript{42} Purulent sputum contains both DNA and large amounts of broad-spectrum protease, both products of neutrophils. DNA prevents the protease from rapidly destroying mucins. If DNA is enzymatically removed, mucin becomes vulnerable to protease attack and is then rapidly hydrolyzed by the protease, leading to mucolysis.\textsuperscript{44–46} RhDNase greatly reduces viscosity of purulent CF-sputum in a concentration-dependent manner. This reduction is associated with shortening of DNA-fragments in sputum.\textsuperscript{47} RhDNase also improves surface properties of CF sputum, as demonstrated by a decrease in the contact angle.\textsuperscript{43} In CF, rhDNase is also able to increase the free water content and alter the phospholipid profile of mucus, with a related improvement in mucus transportability.\textsuperscript{48} Finally, while rhDNase improves ciliary and/or cough clearance in in vitro models\textsuperscript{43,48,49} small in vivo studies in CF patients were unable to demonstrate such improvements in response to short courses of rhDNase.\textsuperscript{50,51}

**Rationale to Use rhDNase in Non-CF Lung Diseases**

RhDNase was specifically developed for patients with CF. Yet it could also be a rational therapy for other
childhood lung diseases involving mucus plugging or impaired mucociliary clearance, in which neutrophilic airway inflammation or increased DNA content of mucus is present.52 Neutrophilic inflammation is seen in adults with stable and acute asthma,53,54 in asthmatic children,55,56 in infants with respiratory syncytial virus (RSV)-bronchiolitis,57 and in children with PCD.58 Increased DNA content has been demonstrated in sputum of adults with stable53 and acute asthma,54 and in bronchoalveolar lavage fluid of infants with RSV-bronchiolitis.59

**Randomized Controlled Trials of rhDNase in Non-CF Lung Diseases**

Efficacy of rhDNase has mainly been studied in patients with CF.15,60–62 No more than four RCTs have been performed in non-CF pediatric patients (Table 3).59,63–65

**RSV Bronchiolitis**

Two RCTs have assessed efficacy of nebulized rhDNase in infants hospitalized with RSV bronchiolitis. The first is that by Nasr et al.59 in 75 infants treated with 2.5 mg rhDNase or placebo once daily up to 5 days (or until discharge). Chest X-ray scores in the rhDNase group significantly improved, whereas those in the placebo group significantly worsened. Clinically relevant endpoints such as length of stay and respiratory symptoms did not differ between groups. Only 60% of patients received supplemental oxygen, indicating that a large proportion of children had only mild bronchiolitis, and perhaps limited room for improvement.

The second is a study by our group in which we assessed the efficacy of 2.5 mg rhDNase twice daily in 225 oxygen-dependent infants hospitalized with RSV bronchiolitis.63 RhDNase did not reduce length of hospital stay, and did not influence clinical improvement or numbers of intensive care admissions. There was a trend, however, toward a longer duration of supplemental oxygen in the rhDNase treated group. We speculated that this might have been on account of these young infants’ difficulty in expectorating liquefied mucus, as they cannot cough as forcefully as older children and do not receive airway clearance therapy.

**Mechanically Ventilated Children**

Riethmueller et al.64 studied 100 children ventilated post-operatively after elective surgery for congenital heart disease. Prophylactic therapy with endotracheal rhDNase, twice daily in doses of 0.2 (children with body weight <5 kg) or 0.1 mg/kg, or placebo was given until extubation. Numbers of children requiring reintubation, the primary endpoint in this study, did not differ significantly (3 vs. 4 children). However, rhDNase did reduce ventilation time, incidence of atelectasis, length of stay on the pediatric intensive care unit, and mean costs.

**Asthma**

Boogaard et al.65 assessed the efficacy of adding a single dose of 5 mg rhDNase to standard treatment in the emergency room in 121 children with a moderate-to-severe acute asthma exacerbation. RhDNase had no effect on the asthma score over the study period of 24 hr, number of bronchodilator treatments, time until discharge, and duration of oxygen supplementation.

**Observational Studies of rhDNase in Non-CF Lung Diseases**

Several uncontrolled observations in non-CF patients report beneficial effects of rhDNase in children with atelectasis, (acute) asthma and PCD, but RCTs in these patient groups are lacking (Table 3).

**Atelectasis/Mucus Plugging**

Atelectasis is a common complication of different respiratory diseases. Impressive results of atelectasis treatment with rhDNase have been reported in the following observational studies. Gershon et al.66 reported resolution of a therapy-resistant atelectasis that had been present for 21 months in an asthmatic child. El Hassan et al.67 reported improved chest radiographs, oxygen requirement, ventilator settings, blood gas values, and findings at physical examination in mechanically ventilated premature neonates suffering from atelectasis. RhDNase treatment also improved ventilator settings, oxygen requirement, and sputum appearance in a series of ventilated, low birth weight infants with early BPD with acute pneumonia or mucus plugging.68 It was also reported to have beneficial effects on chest radiographs, respiratory rate, blood gas values, and oxygen requirement in a large series (n = 30) of hospitalized children with atelectasis.69 Finally, in another series, rhDNase improved findings on physical examination, blood gas values, chest radiographs, and oxygen requirement in infants with severe RSV bronchiolitis and atelectasis.70

In contrast, others found no clinical or radiological improvement after rhDNase treatment in mechanically ventilated children with an atelectasis.71 Kupeli et al.72 reported even new atelectatic areas after rhDNase treatment in one premature infant with recurrent atelectasis, perhaps due to profuse secretions that could not be expectorated efficiently. Hendriks et al.69 reported that 3 out of 30 children showed temporary clinical deterioration with desaturations due to increased airways obstruction immediately after endotracheal administration of rhDNase.
<table>
<thead>
<tr>
<th>Disease, patient characteristics</th>
<th>Study design</th>
<th>N</th>
<th>Age mean or median (range)</th>
<th>Dose of rhDNase, mode of administration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV bronchiolitis, hospitalized infants</td>
<td>RCT&lt;sup&gt;20&lt;/sup&gt;</td>
<td>75</td>
<td>5 (0.3–24) months</td>
<td>2.5 mg rhDNase once daily until discharge (max. 5 days); nebulization</td>
<td>RhDNase versus placebo group: chest X-ray score: improvement of 0.46 versus worsening of 0.66 points ($P &lt; 0.001$); length of stay: 3.3 versus 3.3 days ($P = 0.97$) No effect on symptom score</td>
</tr>
<tr>
<td>RSV bronchiolitis, hospitalized infants</td>
<td>RCT&lt;sup&gt;30&lt;/sup&gt;</td>
<td>225</td>
<td>2.2 (0.4–12.8) months</td>
<td>2.5 mg rhDNase twice daily until discharge; nebulization</td>
<td>RhDNase versus placebo group: length of stay: 4.4 versus 3.8 days ($P = 0.19$); duration of oxygen supplementation: 2.6 versus 2.0 days ($P = 0.07$) No effect on symptom score and number of intensive care admissions</td>
</tr>
<tr>
<td>Mechanical ventilation after elective heart surgery</td>
<td>RCT&lt;sup&gt;44&lt;/sup&gt;</td>
<td>100</td>
<td>Median 3.6 months (5 days to 2.5 years)</td>
<td>0.2 mg/kg rhDNase (&lt;5 kg), 0.1 mg/kg rhDNase (≥5 kg) twice daily until extubation; endotracheal instillation</td>
<td>RhDNase versus placebo group: reintubation rate: 7% versus 9%; OR: 0.77 (CI: 0.11–4.9); incidence of atelectasis: 6 versus 17; OR: 0.27 (CI: 0.08–0.84); length of PICU stay: 7 versus 8 days; 25% reduction (CI: 4–42%); ventilation time: 52 versus 82 hr; 24% reduction (CI: 3–44%); Costs: ≤1,490 lower; 23% reduction (CI: 1–41%) No effect on time till discharge, duration of oxygen supplementation and number of bronchodilator treatments in the first 24 hr</td>
</tr>
<tr>
<td>Mechanical ventilation after elective heart surgery</td>
<td>RCT&lt;sup&gt;45&lt;/sup&gt;</td>
<td>121</td>
<td>4.5 (2.0–16.3) years</td>
<td>5.0 mg rhDNase, single dose following the second dose of bronchodilators; nebulization</td>
<td>RhDNase versus placebo group: asthma score (scale: 0–15) after 1 hr: mean improvement (-8) versus 0 points ($P = 0.23$); asthma score over first 24 hr: mean improvement 4.1 versus 3.9 points ($P = 0.40$) No effect on time till discharge, duration of oxygen supplementation and number of bronchodilator treatments in the first 24 hr</td>
</tr>
<tr>
<td>Asthma and chronic atelectasis</td>
<td>CS&lt;sup&gt;69&lt;/sup&gt;</td>
<td>1</td>
<td>7 years</td>
<td>2.5 mg rhDNase twice daily for 3 weeks; nebulization</td>
<td>Improved chest X-ray</td>
</tr>
<tr>
<td>Atelectasis in premature neonates during mechanical ventilation</td>
<td>CS&lt;sup&gt;70&lt;/sup&gt;</td>
<td>3</td>
<td>27–30 weeks (postconceptional age)</td>
<td>1 mg/m&lt;sup&gt;2&lt;/sup&gt; rhDNase, single dose, endotracheal instillation; 2.5 mg rhDNase twice daily for 3 days; nebulization</td>
<td>Improved chest X-ray, oxygen need, ventilator settings, PaCO&lt;sub&gt;2&lt;/sub&gt;, and physical examination</td>
</tr>
<tr>
<td>Evolving BPD, pneumonia and/or mucus plugging in extremely low birth weight infants</td>
<td>CS&lt;sup&gt;69&lt;/sup&gt;</td>
<td>7</td>
<td>27–35 weeks (postconceptional age)</td>
<td>2.5 mg rhDNase twice daily until improvement; endotracheal instillation</td>
<td>Improved ventilator settings, FIO&lt;sub&gt;2&lt;/sub&gt;, and sputum thickness</td>
</tr>
<tr>
<td>Atelectasis in hospitalized patients</td>
<td>CS&lt;sup&gt;80&lt;/sup&gt;</td>
<td>30</td>
<td>1.6 (0.1–11) years</td>
<td>2.5 mg rhDNase twice daily until improvement; endotracheal instillation</td>
<td>Improved respiratory rate, PaCO&lt;sub&gt;2&lt;/sub&gt;, FIO&lt;sub&gt;2&lt;/sub&gt;, and chest X-ray score</td>
</tr>
<tr>
<td>Severe RSV–bronchiolitis and atelectasis</td>
<td>CS&lt;sup&gt;70&lt;/sup&gt;</td>
<td>5</td>
<td>5–54 weeks</td>
<td>2.5 mg rhDNase twice daily for 2 days; nebulization</td>
<td>No effect on heart rate</td>
</tr>
<tr>
<td>Atelectasis during mechanical ventilation</td>
<td>CS&lt;sup&gt;71&lt;/sup&gt;</td>
<td>7</td>
<td>7 months to 2 years</td>
<td>4 mg/m&lt;sup&gt;2&lt;/sup&gt; rhDNase twice daily for 2 days; endotracheal instillation</td>
<td>Improved physical examination, PaCO&lt;sub&gt;2&lt;/sub&gt;, chest X-ray, oxygen need, and respiratory rate</td>
</tr>
<tr>
<td>Recurrent atelectasis in premature neonate with during mechanical ventilation</td>
<td>CS&lt;sup&gt;72&lt;/sup&gt;</td>
<td>1</td>
<td>33 weeks (postconceptional age)</td>
<td>0.2 mg rhDNase once daily for 5 days; nebulization</td>
<td>No effect on PaO&lt;sub&gt;2&lt;/sub&gt;/FIO&lt;sub&gt;2&lt;/sub&gt;, PaCO&lt;sub&gt;2&lt;/sub&gt;, PIP, volume of bronchial secretions, and chest X-ray</td>
</tr>
<tr>
<td>Status asthmatics and atelectasis</td>
<td>CS&lt;sup&gt;73&lt;/sup&gt;</td>
<td>1</td>
<td>7 years</td>
<td>10 mg rhDNase in 20 ml saline, two doses; endotracheal instillation</td>
<td>Improved chest X-ray, tidal volume, and gas exchange ratio</td>
</tr>
<tr>
<td>Life threatening asthma (without atelectasis)</td>
<td>CS&lt;sup&gt;74&lt;/sup&gt;</td>
<td>1</td>
<td>3 years</td>
<td>2.5 mg rhDNase in 10 ml saline, single dose; endotracheal instillation</td>
<td>Improved peak airway pressure/expired tidal volume, and blood gas</td>
</tr>
<tr>
<td>Acute severe asthma</td>
<td>CS&lt;sup&gt;75&lt;/sup&gt;</td>
<td>3</td>
<td>11–15 years</td>
<td>2.5 mg rhDNase, single dose; nebulization</td>
<td>Improved lung function, and efficacy of cough</td>
</tr>
<tr>
<td>Status asthmatics and atelectasis</td>
<td>CS&lt;sup&gt;76&lt;/sup&gt;</td>
<td>1</td>
<td>8 years</td>
<td>2.5 mg rhDNase in 10 ml saline, single dose; bronchoscopic instillation</td>
<td>Improved bronchoscopic view, and chest X-ray</td>
</tr>
<tr>
<td>Kartagener’s syndrome</td>
<td>CS&lt;sup&gt;77&lt;/sup&gt;</td>
<td>1</td>
<td>14 years</td>
<td>2.5 mg rhDNase once daily for 4 months; nebulization</td>
<td>Improved lung function, cough, and sputum volume</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>CS&lt;sup&gt;78&lt;/sup&gt;</td>
<td>1</td>
<td>3 weeks</td>
<td>2.5 mg rhDNase once daily for 7 months; nebulization</td>
<td>Improved respiratory rate, dyspnea, retraction, nocturnal pulse oximetry, and lung function</td>
</tr>
<tr>
<td>Plastic bronchitis in acute chest syndrome of sickle cell disease</td>
<td>CS&lt;sup&gt;79&lt;/sup&gt;</td>
<td>1</td>
<td>7 years</td>
<td>2.5 mg rhDNase in 20 ml saline, single dose; bronchoscopic instillation</td>
<td>Improved oxygenation index, chest X-ray, and bronchoscopic removal of mucus plugs</td>
</tr>
</tbody>
</table>

N, number of patients; RCT, randomized controlled trial; CS, case series or case report; PICU, pediatric intensive care unit; PaCO<sub>2</sub>, partial pressure of arterial CO<sub>2</sub>; PaO<sub>2</sub>, partial pressure of arterial O<sub>2</sub>; FIO<sub>2</sub>, fraction of inspired oxygen; PIP, positive inspiratory pressure; OR, odds ratio; CI, 95% confidence interval.
Asthma

Several case reports describe the effect of rhDNase administered bronchoscopically, endotracheally or by nebulization in children with severe acute asthma unresponsive to conventional therapy. Intervention with rhDNase was associated with improved ventilator settings, improved arterial blood gas values, improved lung function, more effective coughing, and resolution of atelectasis.

Primary Ciliary Dyskinesia

Two case reports suggest that rhDNase could be beneficial in children with PCD. The first describes a 14-year-old girl with suppurative lung disease secondary to PCD with worsening spirometry and intractable gastrointestinal symptoms despite antibiotics, physiotherapy, bronchodilators, and nebulized isotonic saline solution. Administration of nebulized rhDNase was associated with improved oxygenation, respiratory symptoms and lung function. The second describes a 3-week-old neonate with PCD and severe persisting respiratory symptoms and oxygen dependency despite antibiotics, physiotherapy, bronchodilators, and nebulized isotonic saline solution. Nebulization with rhDNase she showed less cough and sputum volume, less gastrointestinal symptoms and improved lung function. The possible mode of action of rhDNase in PCD patients is unclear; their sputum clearance largely depends on effective cough, and one could argue that reduced sputum viscosity alone could even further impair sputum clearance. One possible explanation, as yet unproven, is that mucusolytic would intensify antibiotic penetration and bacterial killing in the airways, thereby improving lung function and clinical condition.

Other Respiratory Diseases

In a child with sickle cell disease with plastic bronchitis in acute chest syndrome, saline lavage, suction and physical therapy could not remove mucous plugs. Fragmented mucous plugs could be cleared away, though, following bronchoscopic instillation of rhDNase, and oxygenation index and chest X-ray improved immediately.

HYPERTONIC SALINE

Mode of Action

Nebulized hypertonic saline has been used to facilitate mucus clearance mainly in CF patients. Different potential mechanisms of action have been postulated. By breaking the ionic bonds within the mucus gel, hypertonic saline reduces the degree of crosslinking and entanglements, resulting in lower viscosity and elasticity. With chronic infection, mucin macromolecules develop fixed negative charges, which increases repulsion. Addition of hypertonic saline will raise the ionic concentration in mucus and bring about a conformational change by shielding the negative charges—thereby reducing repulsion. This would result in a more compact mucus macromolecule, and more effective clearance. In addition, hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating secretions and thereby improving mucus rheology. While the effect of hypertonic saline on airway surface liquid thickness, and consequently on mucus layer hydration, is short lived in healthy airways (10 min), it is much greater and longer lasting in CF-airways, perhaps because the dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) cannot transport excess salt and water from the airway surface.

In addition, it has been suggested that airway surface liquid hyperosmolarity will release mediators capable of enhancing ciliary activity. Mucoelasticity in vitro and improves predicted cough clearability.

Randomized Controlled Trials of Hypertonic Saline in Non-CF Lung Diseases

As with the other mucoactive agents, nebulized hypertonic saline has been mainly studied in CF patients. Our literature search revealed only three small, RCTs assessing efficacy of hypertonic saline in children with respiratory disease other than CF (Table 4).
<table>
<thead>
<tr>
<th>Disease, patient characteristics</th>
<th>Study design</th>
<th>N</th>
<th>Age mean or median (range)</th>
<th>Dose of hypertonic saline solution, mode of administration</th>
<th>Reported results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral bronchiolitis (80% RSV +, ambulatory setting)</td>
<td>RCT³⁹</td>
<td>65</td>
<td>12.5 (3–24) months</td>
<td>2 ml 3% saline solution and 5 mg of terbutaline, 3 times a day for 5 days; nebulization</td>
<td>Hypertonic saline versus placebo group: Symptom score (scale 0–12) on 2nd day: mean improvement 2.7 versus 1.2 points ($P &lt; 0.05$); Symptom score on 3rd to 5th day: improvement greater in HS group ($P &lt; 0.05$) No effect on chest X-ray score, and hospitalization rate</td>
</tr>
<tr>
<td>Viral bronchiolitis (87% RSV +, hospitalized infants)</td>
<td>RCT⁴⁰</td>
<td>52</td>
<td>2.9 (0.5–12) months</td>
<td>4 ml 3% saline solution and 1.5 mg epinephrine; 3 times a day until discharge; nebulization</td>
<td>Hypertonic saline versus placebo group: Length of hospital stay: 3 ($±1.2$) versus 4 ($±1.9$) days ($P &lt; 0.05$) Improved symptom score 30 min after inhalation No effect on chest X-ray score, and symptom score over time</td>
</tr>
<tr>
<td>Viral bronchiolitis, hospitalized infants</td>
<td>RCT⁴¹</td>
<td>42</td>
<td>2.6 ($±1$) months</td>
<td>4 ml 3% saline solution and 1.5 mg epinephrine, 3 times a day until discharge; nebulization</td>
<td>Hypertonic saline versus placebo group: Length of hospital stay: 2.6 ($±1.4$) versus 3.5 ($±1.7$) days ($P &lt; 0.05$) Improved symptom score 30 min after inhalation No effect on symptom score over time</td>
</tr>
</tbody>
</table>

N, number of patients; RSV, respiratory syncytial virus; RCT, randomized controlled trial; HS, hypertonic saline.
design, Mandelberg et al. compared the effect of epinephrine in 3% saline solution with that of epinephrine in normal saline solution in 52 infants hospitalized with RSV-bronchiolitis. Treatment was thrice daily until discharge. The group receiving the 3% solution stayed significantly shorter in hospital than did the control group (4 vs. 3 days). Information on numbers of infants requiring supplemental oxygen and duration of oxygen supplementation is not provided. Pre-inhalation clinical scores did not differ between groups, but the 3% saline group showed greater improvement in clinical scores 30 min after inhalation. The same authors repeated this study in an additional 41 children, with similar results.

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

Our MEDLINE search revealed scarce literature on the efficacy of the mucoactive agents NAC, rhDNase and hypertonic saline in children with non-CF lung disease. There is a predominance of uncontrolled observations that suggest beneficial effects of mucoactive agents in different lung diseases. We expect there is a likely effect of publication bias, as uncontrolled observations of unfavorable findings are rarely published. For most of these diseases no RCTs have been conducted to confirm or refute these positive findings.

NAC and Other Sulfhydryl Compounds

There is no solid evidence to support the use of inhaled or oral NAC or other sulfhydryl compounds in children with respiratory tract disease. The few published RCTs in non-CF pediatric patients were of crossover design and of short duration. They showed no effects at all or just futile effects of doubtful clinical significance. As oral NAC does not penetrate into airway secretions, it seems unlikely that any effects are the result of mucolysis. A potential drawback of inhaled NAC in children with airway hyperresponsiveness is the risk of bronchospasm. Observational studies also reported cyanotic spells and asphyxia after intratracheal and oral NAC, respectively. Despite this lack of supporting literature, NAC is widely prescribed for children with various respiratory diseases.

RhDNase

Two RCTs in infants with moderate-to-severe RSV bronchiolitis, and one RCT in children with a moderate-to-severe asthma exacerbation demonstrated no clinical benefits of rhDNase. One RCT showed shorter stay on the intensive care unit, and lower incidence of atelectasis in children ventilated post-operatively. Additional trials are needed to confirm these findings. Anecdotal evidence suggests that rhDNase could be beneficial in several childhood lung diseases with impaired MCC, such as acute severe life-threatening asthma, or atelectasis during mechanical ventilation. Still there is an obvious need for confirmation from well-designed RCTs with clinically relevant endpoints before rhDNase can be recommended in non-CF lung disease.

Hypertonic Saline

Efficacy of hypertonic saline in non-CF patients has been studied in only three small RCTs in infants with RSV bronchiolitis, all conducted by the same research group. They reported a beneficial effect on length of hospital stay and symptoms. Although promising, these results need to be confirmed in larger trials.

Recommendations for Future Research

NAC and Other Sulfhydryl Compounds

There is an evident imbalance between the widespread use of NAC as a mucolytic and the lack of data to support this practice. Based on the current literature any mucolytic effect of oral and inhaled NAC in patients with lung disease seems unlikely. Yet, its anti-oxidant properties could be therapeutically effective. Indeed, a recent, small, phase I study showed that high-dose oral NAC can modulate redox and inflammatory imbalances of CF airway disease. Therefore, future studies would do well to focus on the efficacy of (high dose) oral or intravenous NAC in pediatric lung disease with major involvement of airway inflammation, such as CF and severe persistent asthma.

RhDNase

Many case reports have suggested a potential role for rhDNase in non-CF pediatric lung diseases with severe airways obstruction or mucus plugging. Future RCTs should establish whether rhDNase is effective in children with severe acute and severe persistent asthma or with persistent atelectasis, in mechanically ventilated children with atelectasis and in infants with severe RSV-bronchiolitis requiring intensive care. Trials in children with severe acute asthma requiring intensive care obviously require multi-center collaboration for sufficient power. It might as well be worthwhile to assess the efficacy of rhDNase during airways infections in children with impaired mucociliary clearance due to an anatomical airway abnormality, such as malacia. Because rhDNase is an expensive drug, such studies should also take into account cost-effectiveness aspects of this treatment.

Hypertonic Saline

Hypertonic saline reduced length of stay and relieved symptoms in infants with RSV in 3 small RCTs. Larger
RCTs are warranted to confirm these findings. It would also be of interest to explore the effect of inhaled hypertonic saline on symptoms, admission rate or length of hospital stay in children with (viral) respiratory tract infections other than RSV, or with recurrent or chronic bronchitis.

In general, future studies should also report if physiotherapy was used as an adjunct of treatment with mucoactive agents. Although evidence on the efficacy of physiotherapy in (pediatric) lung disease is lacking, it is theoretically plausible that an increase in mucus secretion or clearance should be accompanied by an effective cough and airway clearance.

In conclusion, although the pathophysiology of airway mucus secretion and clearance has been elucidated to some extent, and new mucoactive agents are being developed and tested in adults, there is also still an obvious need for clinical studies in pediatric lung disease using already available mucoactive agents. Of these, rhDNase and hypertonic saline seem to bear most promise. We propose future RCTs may answer the unresolved questions on the efficacy of mucoactive agents in pediatric lung disease. Until then, we must assume the widespread use of compounds such as NAC in children with respiratory illness is not evidence based, and should probably be abandoned.

ACKNOWLEDGMENTS

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