Case Report
Intrapleural administration of DNase alone for pleural empyema

Vladimir Bobek1,2,3, Andrzej Majewski4, Katarina Kolostova1, Adam Rzechonek5,6, Robert Lischke3, Jan Schutzner3, Grzegorz Kacprzak5

1Department of Laboratory Genetics, University Hospital Kralovske Vinohrady, Prague, Czech Republic; 2Department of Histology and Embryology, Wroclaw Medical University, Wroclaw, Poland; 33rd Department of Surgery, First Faculty of Medicine Charles University in Prague and University Hospital Motol, Czech Republic; 4Department of Thoracic Surgery, Nottingham City Hospital, Nottingham, UK; 5Department of Thoracic Surgery, Wroclaw Medical University, Wroclaw, Poland; 6Wroclaw Thoracic Surgery Centre, Lower Silesian Centre of Lung Diseases, Wroclaw, Poland

Received September 12, 2015; Accepted November 14, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Introduction: Pleural empyema is a severe complication of various diseases. The essential is the inserting a drain into the pleural cavity and evacuation of the pus. Sometimes the pus is very thick and its evacuation and re-expansion of the lung is very difficult. Methods: We report a group of 10 patients with intrapleural administration of Pulmozyme (dornase alpha) in dosages of either 2.5 mg once or on two separate occasions. All of the patients had a chest tube inserted into the pleural cavity. Measurement of viscosity was done before and after the instillation of the dornase alpha. Results: In six patients dornase alfa was introduced into the pleural cavity once. Three of them received this on the 4th whilst the rest were treated with the agent on the 6th day. Four patients received the dornase alpha twice because of the small amount of drainage fluid after the previous instillation. Five patients were discharged from hospital with complete re-expansion of their lungs. Two patients were qualified for a surgical operation since the lung was trapped and did not re-expand. Three patients had to be discharged with a drain as a result of incomplete re-expansion of the lung. In all the patients the density of the pus after administering the dornase alpha decreased and the amount of the pus drainage increased. Conclusions: Dornase alpha may be used in some patients with pleural empyema with good results.

Keywords: Pleural empyema, lung, viscosity, deoxyribonuclease, DNase, pulmozyme, dornase alpha

Introduction
Empyema is a collection of pus inside a body cavity and is a severe complication of many diseases. Management of this complication is difficult and should comprise general and local treatment. The general procedure is mainly based on administering wide-spectrum antibiotics. Local management depends on the general condition, but in all cases the essential procedure comprises inserting a drain into the pleural cavity and evacuating the pus. In some cases the pleural fluid is very thick and becomes loculated and its evacuation and re-expansion of the lung is very difficult. The use of intrapleural enzymes to aid drainage was first described in 1949 by Tillett and Sherry using a mixture of streptokinase (fibrynolitic) and deoxyribonuclease (DNase), [1]. In recent years a purified streptokinase has come into widespread use, but some studies suggest that it has little effect on pus viscosity. Some authors announced that recombinant human DNase (rhDNase) reduces pus viscosity and may be more useful in treatment [1-4]. There is emerging evidence that combination of intrapleural fibrinolytic agent with DNase is significantly superior to use as a single agent or placebo in improving pleural fluid drainage in patients with pleural space infection [5]. On the other hand there are case studies reporting excellent effect when DNase alone was used in treatment of pleural empyema [2, 4].

Here, we report a study of intrapleural administration of dornase alfa, a highly purified solution
of recombinant human deoxyribonuclease (Pulmozyme, Hoffman-La Roche AG), with longer application time than in earlier studies.

**Material and methods**

Ten patients treated for pleural empyema in Wroclaw Thoracic Surgery Centre were qualified for the application of dornase alfa into the pleural cavity. Pleural empyema did appear in all the cases as a complication of pneumonia. All patients had a chest tube inserted into the pleural cavity and suction was applied at minus 20 cm of H$_2$O column.

The qualification criteria were difficulties in evacuation of the pus due to density and re-expansion of the lung. The application was in dose 2.5 mg of dornase alfa in 50 ml of normal saline instilled into the pleural cavity. The tube was then clamped for four hours after the instillation. During this period the patient was advised to change position (lateral, supine, and face down). Three patients received dornase alfa on the fourth day, with 3 others receiving dornase alfa on the sixth day. Four were treated with the medication twice on the fourth and sixth day. CT of the chest was performed before the treatment. All patients had chest X-ray and CT of the chest performed to exclude malignancies. The Chest x-ray was taken the next day after the insertion of the tube into the pleural cavity, the following day after the installation of

---

**Figure 1.** Drainage of pus according to the patients (Patients are shown as 1-10).

**Figure 2.** X Ray pictures before and after treatment of empyema by DNase.
dornase alfa into the pleural cavity, before removing and day after removing the drain from the chest.

To measure viscosity a 2 ml medical syringe fitted with 1.2x40 (18 G x 1 1/2) needle was used. Viscosity was measured before instillation of the dornase alfa and after instillation of the first, and I some cases the second dose of dornase alfa.

**Results**

In all the patients the density of the pus after administering dornase alfa decreased and amount of drained pus increased. In 6 patients dornase alfa was introduced into the pleural cavity once. Three of them received dornase alfa on the 4th day, 3 on the 6th day. Four patients received dornase alfa twice because of the small amount of drainage fluid on the day after the first instillation of dornase alfa and lack of improvement on controlled chest x-ray (Figure 1).

Five patients were discharged from hospital after removing the drains. The control x-ray showed full re-expansion of the lung (Figure 2). One patient from this group was treated in Intensive Care Unit because of cerebral stroke during the hospitalization. The patient made slow but positive recovery and was transferred back to the ward after three weeks.

Two patients were qualified for surgical operation, as a result of trapped lung. The first patient received dornase alfa once on the 6th day and the second one twice on the days 4 and 6 with poor effect. Thoracotomy and decortication of the lung were performed. Those patients were treated successfully with decortication of the lung and discharged in good condition with fully re-expanded lung.

Three patients were discharged home with the drains on passive suction. The lungs were not completely re-expanded as were confirmed on control x-ray. These patients were not qualified for an operative procedure because of the poor performance status and/or lack of patients’ consent for the operation. One of them was discharged from hospital on the 19th day with a drain in situ and 3 weeks later the drain was removed due to complete healing the pleural space. Two patients were left with chronic space (Table 1).

**Discussion**

Successful treatment of pleural empyema depends mainly on adequate drainage of pleural cavity. There are other factors which prevent successful drainage by intercostal tube: loculation of the fluid increased viscosity, and fibrosis of the visceral pleura preventing lung re-expansion.

Human recombinant DNase seems to be extremely safe and effective when it is administered by nebulisation in the treatment of cystic fibrosis [6-8]. The experience with fibrinolytic agents, also with DNase, suggests little absorption of enzymes from the pleural cavity where they are used to treat empyema. Zhu Z et al. reported that the combination of alteplase (recombinant tissue plasminogen activator) and rhDNase is more effective in the treatment of rabbit empyema than either agent alone [9].

A multi centre randomized study (MIST-2) of intrapleural application of plasminogen activator (tPA) and DNase in pleural empyema has been completed [5]. In this study the use of a combination of DNase with tPA was significantly superior to the other combinations in improving empyema drainage. Treatment with tPA alone or DNase alone was ineffective. DNase alone seems be associated with increased frequency of surgery.

The use of DNase as a single agent in our study was not associated with increased surgery. In comparison with MIST-2 study we used different timing and dosage of dornase alfa. The MIST-2 study used DNase in a dosage of 5 mg as an intrapleural medication twice daily for first 3 days and each administration was followed by clamping of the drain for 1 hour. In our study we started with application of DNase based on the evacuated quantity of the pus. When we observed significantly lower or evacuation we started application of DNase in dose of 2.5 mg in 50 ml of normal saline into the drain with clamping for 4 hours instead of one. We suppose that there is no reason to use DNase if there is lower viscosity confirmed by adequate quantity of drainage. Similarly we also noted that the time of action of the medication is very important. In first published case study Simpson reported successful treatment of the empyema by intrapleural application time of 4 hours, similar to our study [4]. Our study as well as the above mentioned case
Table 1. Pus volume is reported for patients who received Pulmozyme (dornase alfa) into the pleural cavity once time on the fourth or sixth day or twice on the fourth and sixth day after introducing the tube into the pleural cavity

<table>
<thead>
<tr>
<th>Patient (years old)</th>
<th>1 day ml</th>
<th>2 day ml</th>
<th>3 day ml</th>
<th>3 day drops/min (d/min)</th>
<th>4 day ml/Pulmozyme</th>
<th>5 day ml</th>
<th>5 day drops/min</th>
<th>6 day ml/Pulmozyme</th>
<th>7 day ml</th>
<th>7 day drops/min (d/min)</th>
<th>x-ray</th>
<th>Application of procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (57) years</td>
<td>200 ml</td>
<td>100 ml</td>
<td>100 ml</td>
<td>-</td>
<td>50 ml</td>
<td>50 ml</td>
<td>23 d/min</td>
<td>50 ml/Pulmozyme</td>
<td>450 ml</td>
<td>160 d/min</td>
<td>The lung did not re-expand</td>
<td>Thoracotomy and decortication in 27 day</td>
</tr>
<tr>
<td>2. (59) years</td>
<td>150 ml</td>
<td>150 ml</td>
<td>150 ml</td>
<td>-</td>
<td>100 ml</td>
<td>100 ml</td>
<td>110 d/min</td>
<td>100 ml/Pulmozyme</td>
<td>200 ml</td>
<td>150 d/min</td>
<td>The lung did not re-expand, but residual cavity was small</td>
<td>Discharged from hospital in the 19 day with a carried drain; after 3 weeks the drain was removed</td>
</tr>
<tr>
<td>3. (49) years</td>
<td>400 ml</td>
<td>100 ml</td>
<td>50 ml</td>
<td>-</td>
<td>50 ml</td>
<td>10 ml</td>
<td>70 d/min</td>
<td>50 ml/Pulmozyme</td>
<td>150 ml</td>
<td>200 d/min</td>
<td>The lung was re-expand</td>
<td>Discharged from hospital in the 33 day without the drain</td>
</tr>
<tr>
<td>4. (64) years</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>100 d/min</td>
<td>30 ml Pulmozyme</td>
<td>100 ml</td>
<td>140 d/min</td>
<td>30 ml Pulmozyme</td>
<td>75 ml</td>
<td>200 d/min</td>
<td>The lung was re-expand</td>
<td>Discharged from hospital in the 16 day without the drain</td>
</tr>
<tr>
<td>5. (32) years</td>
<td>300 ml</td>
<td>30 ml</td>
<td>20 ml</td>
<td>56 d/min</td>
<td>20 ml Pulmozyme</td>
<td>400 ml</td>
<td>210 d/min</td>
<td>50 ml Pulmozyme</td>
<td>300 ml</td>
<td>215 d/min</td>
<td>The lung was re-expand</td>
<td>Discharged from hospital in the 29 day without the drain</td>
</tr>
<tr>
<td>6. (46) years</td>
<td>100 ml</td>
<td>100 ml</td>
<td>100 ml</td>
<td>150 d/min</td>
<td>50 ml Pulmozyme</td>
<td>100 ml</td>
<td>160 d/min</td>
<td>50 ml Pulmozyme</td>
<td>120 ml</td>
<td>170 d/min</td>
<td>The lung was re-expand</td>
<td>Discharged from hospital in the 12 day without the drain</td>
</tr>
<tr>
<td>7. (56) years</td>
<td>200 ml</td>
<td>300 ml</td>
<td>200 ml</td>
<td>10 d/min</td>
<td>30 ml Pulmozyme</td>
<td>50 ml</td>
<td>20 d/min</td>
<td>10 ml Pulmozyme</td>
<td>200 ml</td>
<td>80 d/min</td>
<td>The lung did not re-expand</td>
<td>Thoracotomy and decortication in 33 day</td>
</tr>
<tr>
<td>8. (55) years</td>
<td>200 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>30 d/min</td>
<td>40 ml Pulmozyme</td>
<td>100 ml</td>
<td>60 d/min</td>
<td>100 ml</td>
<td>100 ml</td>
<td>-</td>
<td>The lung did not re-expand</td>
<td>Discharged from hospital in the 12 day with a carried drain;</td>
</tr>
<tr>
<td>9. (58) years</td>
<td>300 ml</td>
<td>400</td>
<td>200</td>
<td>86 d/min</td>
<td>150 ml Pulmozyme</td>
<td>250 ml</td>
<td>112 d/min</td>
<td>250 ml</td>
<td>300 ml</td>
<td>-</td>
<td>The lung was re-expand</td>
<td>Discharged from hospital in the 46 day without the drain, (treated in Intensive Care Unit because of cerebral stroke during the hospitalization)</td>
</tr>
<tr>
<td>10. (76) years</td>
<td>300 ml</td>
<td>100 ml</td>
<td>40 ml</td>
<td>40 d/min</td>
<td>30 ml Pulmozyme</td>
<td>100 ml</td>
<td>44 d/min</td>
<td>75 ml</td>
<td>50 ml</td>
<td>-</td>
<td>The lung did not re-expand</td>
<td>Discharged from hospital in the 11 day with a carried drain</td>
</tr>
</tbody>
</table>
study [4] we started treatment only after the dynamics of drainage decreased. Researchers in MIST-2 as well as in animal studies [9, 10] applied DNase with frequency twice per day for 3 days. Their results however showed if DNase used a single agent was ineffective.

We have demonstrated that DNase alone has effect on reducing the quantity of drainage in empyema patients only if the application time was longer than 1 hour and that treatment should commence in decreasing phase of pus evacuation. Our group is too small to draw any final conclusion so further research should be performed.

Conclusion

Human recombinant DNase reduced pus viscosity significantly and may be used in some patients with pleural empyema with good results. Measurement of pleural fluid viscosity using a simple count of drop rate from the syringe could be a useful parameter in evaluation of treatment’s efficacy.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Vladimir Bobek, Department of Laboratory Genetics, University Hospital Kralovske Vinohrady, Srobarova 50, Prague 10-034, Czech Republic. Tel: +420 26713578; E-mail: vbobek@centrum.cz

References


