Bronchoalveolar lavage with trypsin in pulmonary alveolar proteinosis

Yukio Nagasaka, Mika Takahashi, Hisao Ueshima, Yuji Tohda, Sigenori Nakajima

Abstract

Two cases of pulmonary alveolar proteinosis were treated with bronchoalveolar lavage (BAL) via a fiberoptic bronchoscope. Additional clinical improvement was seen when trypsin was added to the lavage fluid. Analysis of effluents in the BAL fluid showed marked reduction of protein constituents with clinical improvement after treatment with trypsin in the lavage. BAL with trypsin was well tolerated.

(Thorax 1996;51:769-770)

Keywords: bronchoalveolar lavage, trypsin, pulmonary alveolar proteinosis.

Bronchoalveolar lavage (BAL) is a recognised treatment for pulmonary alveolar proteinosis (PAP). Lavage of an entire lung may be performed under general anaesthesia.¹⁻³ This procedure may be associated with severe hypoxaemia.⁴ Inhalation of proteolytic enzymes has been tried in PAP with some benefit but is associated with allergic reactions.⁵⁻⁷ We performed BAL with trypsin added to the lavage fluid using a fiberoptic bronchoscope in two patients with PAP.

Case reports

CASE 1

A 45 year old man presented with a history of progressive breathlessness lasting a few months. Corticosteroid therapy had no benefit so he was referred for further management. There was no occupational history. The patient was dyspnoeic and cyanosed, and the chest radiograph showed diffuse alveolar infiltrates predominantly in the perihilar region (figure). Pulmonary function tests showed a restrictive ventilation defect with impaired single breath gas transfer factor. Chemical analysis of the blood revealed increased levels of lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA). The diagnosis of PAP was made by fiberoptic bronchoscopy.

Treatment with BAL was then commenced with the fiberoptic bronchoscope placed in a segmental or lobar bronchus under local anaesthesia and was repeated weekly. An aliquot of 50 ml of warmed and heparinised saline was injected, suctioned, and the aliquot repeated until the patient became uncomfortable with the procedure or the total fluid instilled reached 1000 ml. For the initial seven lavages in which trypsin was not used a mean (SD) of 717 (190.1) ml of heparinised saline was used and the recovery rate was 69(5.9)%. Radiographic and physiological improvement was considered inadequate (table, figure), and nine subsequent lavages included 40 000 USP units of bovine trypsin (Trypsilin, Mochida Pharmaceutical, Tokyo, Japan) per 1000 ml of heparinised saline. A mean (SD) volume of 927(85.4) ml of lavage fluid was used and the recovery rate was 68(7.7)%. After trypsin was added, protein and phospholipid concentrations of the lavage effluent increased and radiographic and physiological improvement followed (table, figure). The total duration of treatment was four months and the patient was well one year after treatment with pulmonary function tests nearly normal.

The Fourth Department of Medicine, Kinki University School of Medicine, 377-2 Ohnohigashi, Osakasayama, Osaka, Japan
Y Nagasaka
M Takahashi
H Ueshima
Y Tohda
S Nakajima

Correspondence to: Dr Y Nagasaka.

Received 17 January 1995
Returned to authors 23 March 1995
Revised version received 5 April 1995
Accepted for publication 21 July 1995

Posteroanterior chest radiographs of case 1 (A) before lavage, (B) after lavage seven times without trypsin, and (C) after lavage nine times with trypsin showing minimal improvement of diffuse pulmonary infiltrate after seven lavages without trypsin and almost complete clearing after nine lavages with trypsin.

Effect of bronchoalveolar lavage (BAL) on pulmonary function, arterial blood gases, and blood chemistry and protein and lipid constituents of lavage effluent in patient 1

	Before lavage*	After lavage without trypsin (7 times)	After lavage with trypsin (2 times)	After lavage with trypsin (9 times)	Four months later	13 months later
FVC (ml)	2120	2230	2310	2300	2640	2870
%FVC	58	61	63	63	72	79
TLC (ml)	2680	2860	3420	3440	3860	3930
%TLC	46	50	60	60	67	69
TLco (mmol/min/kPa)	2.88	2.71	2.71	3.69	5.66	5.76
%TLco	45	42	42	61	83	84
Pao ₂ (kPa)	7.1	5.6	7.2	12.1	14.1	12.9
LDH** (U/ml)	642	469	486	345	285	261
CEA (mg/ml)	7.8	8.0	5.7	2.4	n.t.	n.t.
Analysis of BAL fluid						
Total protein (mg/ml)	13.7	6.2	9.8	1.1	n.t.	n.t.
LDH (U/ml)	746	740	n.t.	267	n.t.	n.t.
CEA (mg/ml)	125.0	71.4	n.t.	42.1	n.t.	n.t.
Phospholipid (nmol/ml)	5233	186	2746	0	n.t.	n.t.
SP-A (mg/ml)	3.5	0.4	3.2	0.1	n.t.	n.t.

* For BAL fluid the data were from the first BAL.

** Normal value for blood LDH is 100–225 IU/l.

FVC=forced vital capacity; TLC=total lung capacity; TLco=carbon monoxide transfer factor; Pao₂=arterial oxygen tension; LDH=lactate dehydrogenase; CEA=carcinoembryonic antigen; SP-A=surfactant protein A; n.t.=not tested.

CASE 2

A 50 year old arc welder who noted increasing dyspnoea and a non-productive cough was diagnosed as having PAP by fiberoptic bronchoscopy. Trypsin inhalation by ultrasonic nebuliser (100 000 units of trypsin in 20 ml of saline for 20 minutes twice daily for three months) did not improve the chest radiograph or arterial blood gas tensions. After repeated segmental or lobar BAL with trypsin (40 000 units per 1000 ml of saline) 11 times during a four month period, Pao₂ increased from 7.1 to 11.7 kPa. Two and 13 years after discharge pulmonary function, arterial blood gas tension, and chest radiographs were normal. Analysis of BAL fluid was not performed.

Discussion

Segmental lavage using fiberoptic bronchoscopy has been used for diagnostic purposes⁸ but reports of its therapeutic use have been limited.⁹ We were not able to find any report describing the use of proteolytic enzyme for lavage in the treatment of PAP.

Arora and colleagues reported temporary clinical improvement but with allergic reactions following parenteral or inhaled trypsin in three cases,⁶ while another case treated with trypsin inhalation underwent clinical resolution.⁵ These allergic reactions were treated with an antihistamine. Riker reported clinical improvement with aerosolised trypsin.⁷ In all of these reports copious sputum production was followed by clinical improvement after inhaled trypsin, but patients are likely to become sensitised to trypsin.

No allergic reaction to trypsin was seen in either of our cases who may be less sensitive to trypsin than others. Another cause of the lack of hypersensitivity is that lavage bypasses the upper airways where allergic reactions are commoner.

Case 1 showed little objective improvement with conventional BAL. The patient improved after trypsin had been added to the lavage fluid and tolerated the procedure well. With supplemental oxygen during BAL there was no hypoxaemia as defined by an oxygen saturation of less than 85% by fingertip oximetry.

In case 1 analysis of the lavage revealed increased protein components.¹⁰ Without trypsin, the protein concentration of the lavage effluent decreased while physiological improvement was small. With trypsin in the lavage fluid, protein and phospholipid concentrations of the lavage effluent increased again and then decreased along with a physiological and clinical improvement.

In the two cases reported here alveolar lavage using trypsin in saline was effective, with no recurrence being noted at 13 years in one case. We conclude that lobar lavage with trypsin is worth assessing in a larger number of patients.

The authors thank Drs Yoshio Kuroki and Toyooki Akino of the Department of Biochemistry of Sapporo Medical College for measurement and analysis of the lavage effluents.

- 1 Kao D, Wasserman K, Costley D, Benfield JR. Advances in the treatment of pulmonary alveolar proteinosis. *Am Rev Respir Dis* 1975;111:361–3.
- 2 Rogers RM, Levin DC, Gray BA, Moseley Jr. LW. Physiologic effect of bronchopulmonary lavage in alveolar proteinosis. *Am Rev Respir Dis* 1978;118:255–64.
- 3 Claypool WD, Rogers RM, Matuschak GM. Update on the clinical diagnosis, management, and pathogenesis of pulmonary alveolar proteinosis (phospholipidosis). *Chest* 1984;85:550–8.
- 4 Altose Md, Hicks RE, Edwards MW. Extracorporeal membrane oxygenation during bronchopulmonary lavage. *Arch Surg* 1976;111:1148–53.
- 5 Brodsky I, Mayock RL. Pulmonary alveolar proteinosis, remission after therapy with trypsin and chymotrypsin. *N Engl J Med* 1961;265:935–8.
- 6 Arora PL, Rogers RM, Mayock RL. Alveolar proteinosis, experience with trypsin therapy. *Am J Med* 1968;44:889–99.
- 7 Riker JB, Wolinsky H. Trypsin aerosol treatment of pulmonary alveolar proteinosis. *Am Rev Respir Dis* 1973;108:108–13.
- 8 Martin RJ, Coalson JJ, Rogers RM, Horton FO, Manous LE. Pulmonary alveolar proteinosis: the diagnosis by segmental lavage. *Am Rev Respir Dis* 1980;121:819–25.
- 9 Brach BB, Harrel JH, Moser KM. Alveolar proteinosis: lobar lavage by fiberoptic bronchoscope technique. *Chest* 1980;69:224–5.
- 10 Honda Y, Takahashi H, Shijubo N, Kuroki Y, Akino T. Surfactant protein-A in bronchoalveolar lavage fluids of patients with pulmonary alveolar proteinosis. *Chest* 1993;103:496–9.