Acute Hypoxemic Respiratory Failure Following Intrapleural Thrombolytic Therapy for Hemothorax*

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Intrapleural instillation of thrombolytic agents has been useful in the treatment of hemothorax when thoracostomy tube drainage is unsuccessful. We present a patient who developed acute hypoxemic respiratory failure following the intrapleural instillation of both streptokinase and urokinase 24 h apart. Hypoxemia most likely resulted from a direct effect of the products of fibrinolysis on the pulmonary circulation.

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Complications of the therapeutic use of intrapleural thrombolytic agents are infrequent. Although intravascular administration has been associated with adult respiratory distress syndrome (ARDS) in two patients,1,2 intrapleural instillation has not been previously reported to lead to pulmonary complications. We recently observed a patient who developed two episodes of severe hypoxemia related to the instillation of two different thrombolytic agents.

CASE REPORT

A 58-year-old man with sick sinus syndrome developed an iatrogenic right hemothorax following placement of a permanent transvenous cardiac pacemaker. Closed thoracostomy tube drainage to suction was not sufficient in completely evacuating the hemothorax.

On the fourth day after tube placement, 250,000 U of streptokinase was instilled intrapleurally. Eight hours following instillation, the patient developed severe hypoxemia and basilar crackles. Physical examination did not suggest a cardiac cause. He remained afebrile and had no hemoptysis or arrhythmias. He had never previously received a thrombolytic agent. Baseline cardiac ejection fraction was 65 percent. The arterial blood gas (ABG) values on 100 percent oxygen were pH of 7.44, Pco2 of 31 mm Hg, and Po2 of 73 mm Hg. Prior to the instillation of streptokinase, the ABG values on 2 L/min nasal cannula O2 were pH of 7.37, Pco2 of 33 mm Hg, and Po2 of 81 mm Hg. The chest radiograph showed bilateral interstitial and alveolar infiltrates, diffuse volume loss, and the previously observed blunting of the right costophrenic angle. Pulmonary artery catheterization revealed a pulmonary artery pressure (PAP) of 24/6 mm Hg, pulmonary capillary wedge pressure (PCWP) of 5 mm Hg, and cardiac output (CO) 6.4 L/min. Fibrinogen level was 489 mg/dl (control, 175 to 400), prothrombin time was 13.3 s (control, 11.4 s), partial thromboplastin time of 22.6 s (control, 25.7 s), and platelet count of 310,000/μl.

Four hours after administration of aerosolized β-agonists,

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intravenous corticosteroids, and diphenhydramine, the patient's condition was improved and ABC values had returned to baseline. The chest tube drained 500 ml of hemorrhagic fluid, but drainage then decreased. Urokinase, 450,000 U, was instilled intrapleurally on the following day. Seven hours after instillation, the patient developed the same adverse reaction and response to treatment as with streptokinase. The chest tube drained 300 ml over the next 2 days and then was removed. One month later, he was asymptomatic, and his chest radiograph had returned to baseline.

**Discussion**

The therapeutic uses of intrapleural thrombolytic agents have been reported for over 40 years.\(^3\) The newer purified agents used to treat empyma and hemothorax have been reported to be safe and effective.\(^4,5\) Adverse effects have been limited to fever, erythema, and edema of the chest wall adjacent to the chest tube, and some decrease in hemoglobin which may be due to the primary process. Two cases of ARDS associated with the use of intravenous and intra-arterial streptokinase have been reported.\(^1,2\) We are unaware of previous reports of severe hypoxemia or pulmonary edema associated with the use of intrapleural thrombolytic agents.

A cardiogenic cause of this patient's acute hypoxic respiratory failure was excluded by the normal PCWP. An immunologic cause may have been suspected if the hypoxemia had followed the use of streptokinase only, but urokinase lacks antigenicity. It is doubtful that both preparations contained impurities that would cause hypoxemia. The only compound common to both preparation was albumin which is not reported to lead to hypoxemia in humans or when infused into animals.\(^6\)

It is unlikely that the patient's hypoxemia was due to alveolar hemorrhage, since he had a mildly elevated fibrinogen level. This is in concert with earlier observations that there are no important measurable effects on systemic fibrinolysis caused by intrapleural instillation of streptokinase.\(^7\) Plasma plasminogen, α2-antiplasmin, fibrinolytic activity, and thrombin time do not change after intrapleural instillation of thrombolytics. In fact, the systemic fibrinogen level is commonly elevated since it is an acute phase reactant, despite an increase in fibrin degradation products (FDP).\(^7\) These FDP are likely generated during fibrinolysis in the pleural space and are then rapidly transferred into the systemic circulation. Rapid systemic uptake has been documented when other agents are instilled intrapleurally.\(^8\)

We believe that this patient's severe hypoxemia resulted from the effect of the products of fibrinolysis on the pulmonary circulation leading to capillary leak pulmonary edema. These products include high molecular weight intermediate products (fragments X and Y), end products (fragments D and E), and various low molecular weight fragments.

The low molecular weight products have been shown to increase vascular permeability.\(^9,10\) Increased permeability is partly suppressed by prior administration of antihistamines, suggesting the peptides are histamine-like or that liberation of histamine from local cells accounts for some of their effect.

Experimental intravenous infusion of FDP fragment D into rabbits produces diffuse pulmonary injury resembling ARDS.\(^8,11\) Pretreatment with antihistamines also attenuates the effect of fragment D on permeability. Infusion of fragment E has significantly less effect on lung vascular permeability.\(^8,12\) In vitro, fragment D reversibly binds to endothelial cells and leads to a retraction-like alteration of the cytokeratins F-actin microfilaments, possibly leading to the vascular permeability changes observed.

Other studies suggest the active factor involved in endothelial injury is the thrombin cleavage product fibrinopeptide B and plasmin cleavage product B91-42 which contains fibrinopeptide B.\(^13\) According to this model, endothelial cell reactive peptides are produced whether the balance tips toward fibrinogenesis or fibrinolysis.

Since FDP have been shown to increase pulmonary vascular permeability and are known to be elevated after intrapleural instillation of thrombolytics, we believe that our patient's acute hypoxic respiratory failure resulted from a direct effect of the products of fibrinolysis on the pulmonary circulation.

**References**

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