Unintentional intramuscular administration of tPA/DNase for pleural infection

Natalia Popowicz1, Michael Nash2 & Y. C. Gary Lee2,3

1Pharmacy Department, Sir Charles Gairdner Hospital, Perth, Australia
2Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia
3Centre for Asthma, Allergy and Respiratory Research, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

Abstract

Intrapleural tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) therapy has recently been shown to improve outcomes in pleural infection in a randomized trial. Published literature, to date, consists of only ∼50 patients who had received tPA/DNase. Safety data of this regimen remain limited. Pleural contents often track along chest drains, but the effect of tPA/DNase on subcutaneous tissues is unknown. We report a patient treated in another center who was unintentionally administered up to six instillations of tPA (10 mg) and DNase (5 mg) intramuscularly via a malpositioned chest drain. The patient experienced minimal discomfort, and there were no signs of tissue inflammation or necrosis on computed tomography. No complications were detected over a 2-month follow-up. Upon transfer, a new pleural drain was inserted and tPA/DNase administered with clearance of his loculated complicated parapneumonic effusion. This case adds to the safety profile of intrapleural tPA/DNase therapy and highlights the importance of correct tube placement.

Introduction

Pleural infection is associated with high morbidity and mortality. Intrapleural tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) therapy has been successfully used in pleural infection to aid drainage of infected pleural fluid, and reduce hospital stay and need for surgical intervention [1]. However, there are only 50 published cases on the use of tPA/DNase therapy and its safety profile has not been fully established. Bleeding due to tPA, for example, remains a concern. Local leakage around drain site is common during tube drainage and/or intrapleural instillation.

Malpositioning is a common complication of tube thoracostomy; therefore, confirmation of tube positioning is important before administering intrapleural treatment [2]. We report the first case of tPA/DNase unintentionally administered intramuscularly via a misplaced chest tube. The patient received up to six doses of tPA/DNase intramuscularly without systemic or local adverse effects. Our case provides valuable information toward the safety profile of this therapy for pleural infection and highlights the importance of correct tube placement and monitoring chest drain position.

Case Report

A 21-year-old man with a history of epilepsy and Asperger’s syndrome presented to another hospital with fever, shortness of breath, cough, and left-sided pleuritic chest pain. He was tachycardic and dyspnoeic. His chest radiograph (CXR) confirmed a left lower lobe pneumonia with an associated pleural effusion.

Despite broad-spectrum intravenous antibiotics with piperacillin/tazobactam and oral azithromycin, the patient remained febrile with a raised C-reactive protein (CRP) (peak 274 mg/L). CXR revealed further accumulation of his left-sided pleural effusion. A diagnostic thoracentesis on day 6 revealed turbid fluid, which was exudative (protein...
54 g/L; lactate dehydrogenase 1738 U/L). Pleural fluid culture was noncontributory.

An 8F intercostal catheter (ICC) was inserted on day 8, which drained 50 mL initially and a further 10 mL over the next 20 h. A post-insertion CXR showed an elevated left hemidiaphragm with the tip of the ICC resting marginally above the level of the hemidiaphragm. No lateral plates were taken.

The attending medical team initiated intrapleural instillations of tPA 10 mg mixed with DNase 5 mg in 20 mL of normal saline via the ICC. Six doses were administered over three days. Only 13 mL was drained over 72 h and the large pleural collection remained unchanged radiologically.

A subsequent computed tomography (CT) scan performed 18 h following completion of tPA/DNase therapy showed the distal end of the ICC was not positioned in the pleural cavity but approximately 30 mm outside it (Fig. 1). The tip of the ICC terminated in a fat plane between the Latissimus dorsi and Teres major, level with the inferior angle of the scapula. Some soft tissue swelling was seen around the distal end of the ICC, presumably because of residual fluid. Although it is possible that drain migration occurred during the course of tPA/DNase instillation, these images together with the lack of fluid drainage (after administration of fibrinolytics) strongly suggested that the majority of tPA/DNase doses were delivered not intrapleurally, but into the subcutaneous tissue/muscles. There were however no evidence of inflammation, necrosis, or other significant complications on CT. Throughout the course of treatment, the patient was relatively asymptomatic, and only experienced some mild local pain from the tPA/DNase instillations.

The patient was transferred to our pleural unit for further management. On arrival, an 18F chest tube was inserted into the left pleural effusion under ultrasound guidance. Only 200 mL drained spontaneously over 24 h and ultrasound confirmed a significant residual collection. Intrapleural tPA/DNase was recommenced the following day. Following two doses of tPA/DNase, 800 mL of pleural fluid was drained in 24 h, paralleled by resolution of the pleural opacities on CXR and normalization of leukocyte count and CRP in peripheral blood. The drain was removed two days later. The patient was followed up to two months with no residual symptoms or radiographic abnormalities (Fig. 2). The site of intramuscular tPA/DNase delivery healed spontaneously.

**Discussion**

There is limited safety information available for the use of tPA and DNase therapy for pleural infection despite the increasing application of this treatment worldwide. tPA has a short half-life and is most commonly administered systemically for thrombolysis in ischaemic strokes or heart disease. DNase is well tolerated when given via inhalation in patients with cystic fibrosis and has been shown to be safe and well tolerated when administered systemically in small studies [3]. The effects of tPA/DNase on muscles or subcutaneous tissues have not previously been reported.

The safety data of combined tPA/DNase delivered intrapleurally are only available in 50 published cases [1, 4,
Intrapleural delivery of solutions/drugs often involves seepage of solution to subcutaneous tissue or along the ICC path, but the safety of tPA/DNase in subcutaneous tissue is not known. This case shows that full doses of tPA/DNase, administered unintentionally to the subcutaneous tissues and/or muscle, caused minimal adverse effects, providing more confidence to the use of this regimen. This case also highlights the efficacy of tPA/DNase therapy in treating complex parapneumonic effusions. Intrapleural administration of fibrinolytics generally stimulates significant fluid production. The absence of fluid drainage after tPA/DNase instillation should raise concerns of catheter blockage or tube malpositioning.

Disclosure Statements
Y.C.G. Lee was a co-investigator of the MIST-2 study, which received unrestricted research fund from Roche UK. He is an advisory board member of Lung Therapeutics, Inc.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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