Off-Label Drug Uses

Alteplase: Pleural Effusion (Parapneumonic) and Empyema in Children

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Parapneumonic effusion (PPE), the accumulation of exudative fluid in the pleural space, may develop in adult and pediatric inpatients with suspected bacterial pneumonia, significantly increasing the risk of morbidity and mortality.¹ The initiation of prompt antibiotic therapy in all patients with suspected infection and the promotion of pleural drainage in certain patients are recommended. The adjunctive use of intrapleural fibrinolytics has been helpful in increasing drainage volume in certain adult patients and is considered one of the acceptable approaches identified for managing pediatric patients. It has been suggested that alteplase (tPA) possesses beneficial characteristics for a fibrinolytic agent used for this purpose: a high fibrin affinity and binding, a short half-life, and activity only in the presence of fibrin (high selectivity and specificity).²

PATIENT POPULATION

Pediatric patients (>3 months) with moderate to high risk pleural effusion or empyema related to pneumonia.

DOSAGE AND DURATION

Various intrapleural dosage regimens have been used: 2 to 5 mg diluted in up to 40 mL of normal saline or 0.1 mg/kg diluted in 10 to 100 mL of normal saline. Maximum doses have ranged from 3 mg to 6 mg.

- 4 mg mixed in 30 to 50 mL of sterile normal saline with dwell time of 1 hour, after which chest tube is placed on continuous suction or -20 cm H₂O. The first dose is administered with chest tube placement; 2 additional doses are administered 24 hours apart for 3 doses over a 48-hour period.^{3,4}
- 2 to 5 mg in normal saline with dwell time of 4 to 6 hours followed by drainage. Treatment is repeated every 12 to 24 hours.⁵
- 0.1 mg/kg (maximum: 3 mg) diluted in 10 to 30 mL normal saline with a dwell time of 45 to 60 minutes, after which chest tube is placed on continuous suction or -20 to -25 cm H₂O. First dose is administered after placement of pigtail catheter, repeated every 8 hours or 3 times daily for approximately 3 to 4 days.^{6,7}
- 0.1 mg/kg (maximum: 6 mg) diluted in 25 to 100 mL of normal saline with dwell time of 1 hour, after which standard water seal suction is resumed. Treatment is repeated once daily.⁸

Various size chest tubes, number of doses, patient positions (still vs rotation), and clamping duration (1 to 6 hours) were utilized.

RESULTS

The use of alteplase in the treatment of PPE has been evaluated in both controlled and noncontrolled settings (eg, retrospective reviews, case series),

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enrolling over 500 patients and demonstrating beneficial reductions in effusion volume, clinical symptoms, hospital stay, and the need for surgical intervention. National and international guidelines recognize adjunctive intrapleural fibrinolytic therapy as an accepted therapeutic option.^{9,10} There are few prospective, randomized, comparative trials with other treatment options. Variations in dosage regimens, including chest tube sizes, patient positioning, and clamp time, make it difficult to determine optimal dosing.

Guidelines

Pediatric Infectious Diseases Society and Infectious Diseases Society of America

Clinical practice guidelines regarding the management of community-acquired pneumonia in infants and children older than 3 months of age suggest that both chest thoracostomy tube drainage with adjunctive fibrinolytic therapy (alteplase or urokinase) and video-assisted thoracoscopic debridement (VATS) are acceptable methods of treatment. The choice of treatment should be based on local expertise (strong recommendation; high-quality evidence). These guidelines strongly recommend that small, uncomplicated PPE may be treated with antibiotic alone and should not be routinely drained (based on moderate evidence). Moderate PPE associated with respiratory distress, large PPE, or documented purulent PPE should be drained. These recommendations are based on a limited number of randomized or randomized controlled trials comparing chest tube drainage with fibrinolysis or VATS. In patients with moderate to large effusions without loculations, a chest tube without fibrinolysis is considered a first-line option (strong recommendation; high-quality evidence).⁹

British Thoracic Society

The British Thoracic Society (BTS) guidelines regarding the management of pleural infections in children present an algorithm for treatment decisions. Antibiotic therapy is recommended for all cases of suspected infected pleural infections. Intrapleural fibrinolytics are recognized to shorten hospital stay and are recommended for any complicated PPE (thick fluid with loculations) or empyema (overt pus). These guidelines also state that there is no evidence that any one of the 3 fibrinolytics (eg, streptokinase, urokinase, or alteplase) are more effective than another; only urokinase has been studied in a randomized controlled trial in children, so it is recommended. Urokinase is not available in the United States.¹⁰

Controlled Trials

In a prospective study, 36 children with empyema were randomized to treatment with VATS or fibrinolytic therapy with intrapleural tPA (4 mg diluted in 40 mL of normal saline). The tPA solution was administered at the time of chest tube placement with a dwell time of 1 hour, after which the tube was placed back to continuous suction. Two additional doses were administered separated by 24 hours for a total of 3 doses in a 48-hour span. The mean ages were 4.8 years and 5.2 years in the VATS and tPA groups, respectively ($P = .77$). There were no significant differences between the 2 groups for clinical outcomes monitored, including length of hospital stay post therapy (6.9 vs 6.8 days; $P = .96$), posttherapy days of oxygen support (2.3 vs 2.3 days; $P = .9$), days to afebrile post therapy (3.1 vs 3.8 days; $P = .46$), or the number of analgesia doses required (22.3 vs 21.4; $P = .90$). Hospital charges were significantly higher in the VATS group (\$11,700 vs \$7,600; $P = .02$). No patient in the tPA group worsened clinically after the initiation of therapy. Two patients in the VATS group required ventilator support; one developed progressive sepsis with eventual temporary renal failure. No patient in either group was readmitted for reasons related to recurrent pulmonary disease. The authors concluded that there were no therapeutic or recovery advantages between VATS and fibrinolysis for the treatment of empyema; however, fibrinolysis may pose less risk of acute clinical deterioration and should be the first-line therapy for children with empyema.³

Noncontrolled Trials

In a retrospective cohort study over a 6-year period (1997 to 2002), 30 children with complicated PPE were treated with either early or late intrapleural tPA and were compared to children with thoracostomy tube drainage alone (control group). Intrapleural tPA was administered as 4 mg/30 to 50 mL normal saline instilled through a chest tube, which was clamped for 1 hour. Early and late administration was defined as the first dose administered at or sooner than 24 hours after diagnosis and more than 24 hours after diagnosis, respectively. A total of 12 children (median age, 44 months) received early tPA treatment (median time of administration after diagnosis, 4 hours; range, 0–21 hours) and 18 (median age, 41 months) received late tPA treatment (median time of administration after diagnosis, 64 hours; range, 28–195 hours). Twenty-three patients were in the control group (median age, 60 months). Monitored clinical outcomes included

total volume and rate of pleural fluid drainage, duration of chest tube placement, and the occurrence of local or systemic bleeding. Total pleural fluid drainage was highest for the late tPA group compared to the tPA and control groups (median volumes, 691 vs 638 vs 360 mL, respectively). The late group values were considered significantly greater than the control group values ($P < .05$). Pleural fluid drainage rates were highest in the early tPA group and were considered significantly different than the control group (median rates, 4 vs 7 vs 3 mL/h, respectively; $P < .01$). The median duration of chest tube placement was also shortest in the early tPA group and was considered significantly different than the late tPA group (84 vs 209 vs 130 hours, respectively; $P < .01$). No episodes of local or systemic bleeding occurred in the children who received tPA. The authors concluded that early intrapleural administration of tPA may be a potentially effective treatment for complicated PPE in children.⁴

In a retrospective review, 71 children (mean age, 5.8 years; range, 6 months to 18.8 years) with PPE or empyema who were treated with percutaneous thoracostomy and intrapleural administration of fibrinolytics (alteplase or urokinase) were evaluated. Fibrinolytic agents were diluted in 25 to 100 mL of normal saline, with the volume arbitrarily selected on the basis of patient age and size and the estimated pleural volume. Urokinase doses ranged from 25,000 to 100,000 IU (concentration of 1,000 IU/mL), and alteplase doses were administered at 0.1 mg/kg (maximum, 6 mg). After administration of the fibrinolytic dose, the thoracostomy tube was clamped for 1 hour. No special positioning of the patient occurred. Fibrinolytic treatment was continued once daily until the fluid output decreased to less than 40 mL/d. Monitored clinical outcomes included pleural thickness, chest opacification upon x-ray, and pleural fluid drainage. The mean number of treatments required was not significantly different between the alteplase- and urokinase-treated patients (2.8 vs 2.3; $P = .14$). The mean hospital stay after treatment was not significantly different between the groups (9.7 vs 9.5 days, respectively; $P = .70$), but the reduction in mean pleural thickness was significantly greater in the alteplase group after treatment (-1.5 vs -0.9 cm; $P = .004$). However, there was no difference in the pleural thickness at or after 1 month of treatment. The reduction in lung opacification after treatment was also significantly greater in the alteplase group (-35.9 vs 23.1; $P = .04$). The mean fluid drainage (output) was also significantly greater in the alteplase group 24 hours after the first treatment (299 vs 165

mL; $P = .007$), 24 hours after the second treatment (319 vs 115.4 mL; $P < .001$), but not 24 hours after the third treatment (234 vs 137 mL; $P = .12$). Mean total volume of fluid drainage was significantly greater in the alteplase group (1,178 vs 501 mL; $P < .001$). Multivariate analysis indicated that greater total fluid output was significantly associated with patient age, larger tube size, and greater volume of drainage during the 24 hours prior to fibrinolytic treatment. The authors concluded that fibrinolytic treatment with alteplase or urokinase facilitates pleural effusion drainage via thoracostomy tube with alteplase producing greater tube output.⁸

SAFETY

Some retrospective reviews of PPE did not observe any bleeding episodes associated with intrapleural tPA administration in children,^{4,7} while others noted minor bleeding in drained pleural fluid in some patients.^{5,8} An isolated case report of intrapleural hemorrhage related to the intrapleural administration of a single dose of tPA (3 mg; 0.1 mg/kg diluted in 30 mL of normal saline) was observed in a 6-year-old boy with pleural effusions.¹¹

THERAPY CONSIDERATIONS

The use of alteplase in the treatment of PPE has been evaluated in both controlled and noncontrolled settings (eg, case series), demonstrating beneficial reductions in effusion volume, clinical symptoms, hospital stay, and the need for surgical intervention. National and international guidelines recognize adjunctive intrapleural fibrinolytic therapy as an accepted therapeutic option. There are few prospective, randomized, comparative trials with other treatment options. Variations in dosage regimens, including chest tube sizes, patient positioning, and clamp time, make it difficult to determine optimal dosing.

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