Thrombolysis In Pulmonary Embolism: An Adolescent With Protein S Deficiency

Terence A. Degan, MD

Pulmonary embolism is rare in nonhospitalized children, and essentially all will have a serious underlying disorder or predisposing factor.[1] This report presents a case of an adolescent boy whose condition was successfully treated with recombinant tissue plasminogen activator (rt-PA); he was subsequently found to have protein S deficiency.

Alteplase (Activase), a recombinant tissue plasminogen activator, was approved in June 1990 by the Food and Drug Administration for use in the management of acute massive pulmonary embolism in adults. Urokinase and streptokinase had both been approved for this indication by 1978. There are no studies comparing thrombolytic therapy (followed by heparin) with heparin alone in children with acute pulmonary embolism.

Case Report

A 15-year-old boy with a history of allergic rhinitis came to the emergency department complaining of a 6-day history of progressive dyspnea and cough. He had been baling hay during this time, and 2 days before admission was prescribed an inhaled bronchodilator. After no response to the bronchodilator was experienced, he sought care at the emergency department. On examination he was a 54-kg adolescent in moderate respiratory distress with cyanosis. He had a respiratory rate of 28/min, a pulse rate of 100 beats per minute, and a temperature of 100.2°F. Auscultation of the chest revealed bilateral decreased breath sounds but no wheezes. A grade II-III/VI systolic murmur that increased with inspiration was heard over the second right intercostal space. The chest roentgenogram was normal (Figure 1), and deep T-wave inversions in leads V_1 though V_3 were found on the electrocardiogram. Arterial blood gas on room air showed a pH of 7.49, pCO_2 of 28.4 mmHg and a pO_2 of 39.8 mmHg.

The initial working diagnosis of status asthma was made, but when a peak expiratory flow rate of 460 L/min was found, a ventilation-perfusion lung scan was ordered (Figure 2). This scan revealed a high probability for massive pulmonary emboli. A subsequent family history revealed that both his brother and mother had been hospitalized for deep venous thrombosis in the past. Also noted was a very minor injury that had occurred to his left calf 2 weeks earlier. Sera was then drawn for proteins S and C, antithrombin III, and anticardiolipin antibody. Next, 70 mg of rt-PA (1.3 mg/kg) was given intravenously at an infusion rate of 2 hours and was immediately followed by an intravenous heparin bolus and infusion. The patient suffered transient chest pain during rt-PA infusion. Two hours later anterior epistaxis was easily controlled with silver nitrate cautery.

Within 3 hours the boy's respiratory rate and pulse rate returned to normal and his dyspnea resolved. The following day findings on a venous duplex ultrasound examination of both legs were completely normal, and an echocardiogram showed mild hypokinesis with an ejection fraction of 72 percent. He noted mild pleuritic chest pains for several days following admission. A follow-up ventilation-perfusion scan showed improvement in the perfusion defects. His daily partial thromboplastin time (PTT) averaged 2.6 times control. His international normalized ratio averaged 2.8 in the 4 days preceding discharge. Aside from the minor anterior epistaxis, he had no bleeding complications. His admission hematocrit was 45.8 percent, and his lowest hematocrit during the 8-day hospital stay was 37.3 percent.

The protein S activity result was 22 percent (normal=65 to 140 percent) acutely and 19 percent (normal=65 to 140 percent) 7 weeks later when he was taking coumadin. His mother's free protein S level was 0.09 U/mL (normal=0.62 to 1.38 U/mL), and total was 1.15 U/mL (normal=1.5 to 3.15 U/mL). She had no other reason for a decreased level, such as receiving

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From a private practice. Address reprint requests to Terence A. Degan, MD, 9755 Lincoln Village Dr, Sacramento, CA 95827.

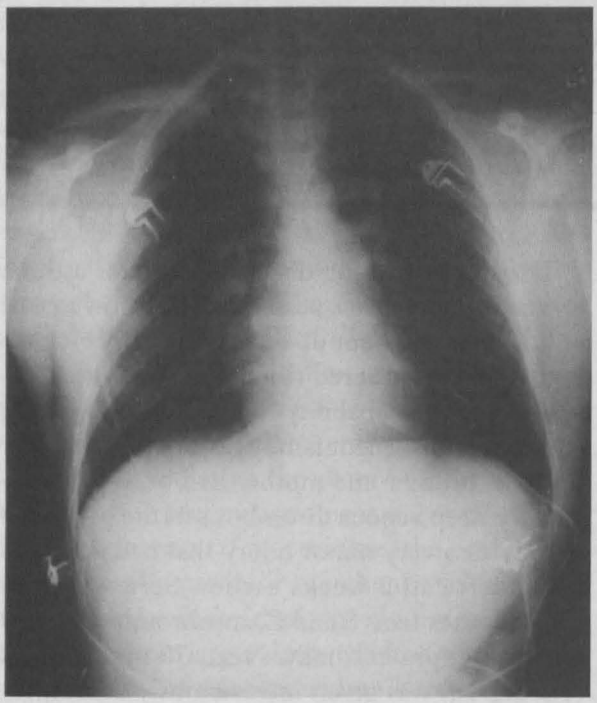

Figure 1. Chest roentgenogram of 15-year-old boy with a pulmonary embolism.

warfarin within 2 weeks, liver disease, nephrotic syndrome, pregnancy, oral contraceptives, or disseminated intravascular coagulation. Three other siblings had normal protein S levels. Unfortunately, the male sibling who had been hospitalized with a deep venous thrombosis refused testing. Our patient was doing well 10 months after discharge on a regimen of coumadin, presumably for life.

Discussion

Whether the dramatic improvement in dyspnea, pulse, and respiratory rate following treatment with rt-PA translated into improved survival or decreased morbidity for this patient is unknown. A study using pooled data from 1974 through 1988 did not show that thrombolytic therapy improved clinically relevant outcomes in patients with pulmonary embolism.[2] Methods have changed, however, to make thrombolytic drug treatment safer — diagnosis of most cases with high-probability pulmonary scans rather than angiography, lower infusion time of 2 hours for rt-PA versus 12 to 24 hours for urokinase and streptokinase, and intravenous route of thrombolytic delivery rather than intraarterial.[3] A recent randomized study of 101 initially hemodynamically stable patients showed improved right ventricular wall motion, decreased right ventricular end-diastolic area, improved pulmonary perfusion, and fewer recurrent pulmonary emboli in patients who received rt-PA compared with those who received heparin alone.[4] A subset of these patients with initial right ventricular hypokinesis and randomized to heparin alone had a high rate of recurrent pulmonary embolism (5 of 18, 2 of whom were the only fatalities in the study). So although thrombolytic therapy has not been proved to decrease mortality, most physicians believe that in the absence of clear contraindications, thrombolytic agents are indicated in the treatment of life-threatening pulmonary embolism.[5]

A pediatric dose for the intravenous administration for rt-PA with a 2-hour infusion time could not be found in a review of the recent literature. The dose of 1.3 mg/kg (70 mg) was chosen empirically by extrapolation from the standard 100-mg adult dose. One article recommended waiting for the PTT to be less than twice the upper limit of normal before starting heparin therapy following the use of thrombolytic drugs.

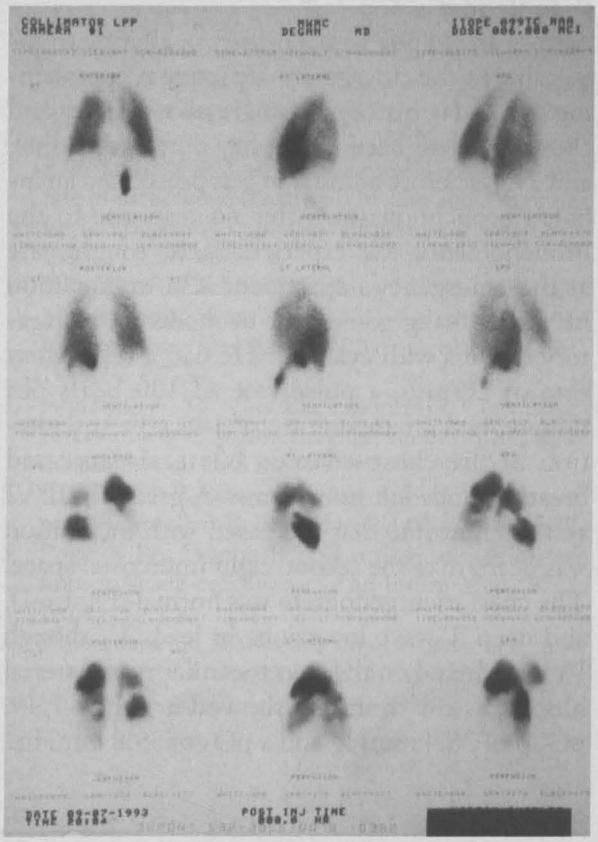

Figure 2. Ventilation-perfusion lung scan, revealing high probability for massive pulmonary emboli.

Heparin therapy and warfarin administration are overlapped for a minimum of 5 days.[6]

Protein S is a cofactor for protein C in fibrinolysis. Congenital deficiency of protein S is inherited in an autosomal dominant manner, and long-term anticoagulation of symptomatic patients reduces the incidence of recurrent thrombosis.[7] The patient's mother has since received anticoagulant therapy with warfarin as an outpatient. To decrease the risk of warfarin skin necrosis associated with protein C or S deficiency, she was given subcutaneous heparin beginning several days before the initiation of warfarin and continuing until adequate anticoagulation was achieved.[7] The heparin theoretically interrupts the cascade of events leading to necrosis by preventing thrombosis of the postcapillary venules.[8]

Summary

Because of the low incidence of pulmonary embolism in children, the therapeutic approach is extrapolated from guidelines for adults.[1] An adolescent boy with a massive pulmonary embolism associated with protein S deficiency was cared for successfully with intravenous thrombolytic therapy using 1.3 mg/kg of rt-PA with a 2-hour infusion time. In the absence of contraindications, most physicians consider using thrombolytic drugs in hemodynamically unstable patients who have a pulmonary embolism. A recent study described a subset of hemodynamically stable patients with right-ventricular dysfunction who also might benefit from thrombolytic therapy.

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