

Complications of Thrombolysis

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Case Summary:

An 88 year-old man with a past medical history of hypertension and paroxysmal atrial fibrillation presented to the emergency department (ED) with a sudden onset of right-sided weakness and difficulty with word-finding. Two hours prior to presentation he was having breakfast with his wife when he suddenly experienced sudden weakness of his right side and his wife noted that he had difficulty speaking.

On physical examination, he was awake and alert. Vitals signs: blood pressure, 141/68 mmHg; pulse, 92 beats/min; respiratory rate, 18 breaths/min; temperature, 98.6°F (37°C). Examination of the head, eyes, ears, nose, and throat was unremarkable. His chest was clear to auscultation bilaterally, and heart examination revealed a regular rhythm with no murmurs. The patient's neurologic exam revealed intact cranial nerves, decreased motor strength and sensation on the right side of the body. His reflexes and cerebellar exam was normal. He was noted to have no dysarthria, but did have a moderate expressive aphasia.

The patient was immediately given 100% oxygen via a nasal cannula; an electrocardiogram demonstrated normal sinus rhythm without ischemia. Initial laboratory studies showed a white blood cell count of 12,000/mm³, hemoglobin 12 g/dL, hematocrit 36%, and platelets 217,000/mm³. The initial prothrombin time was 22 seconds (international normalized ratio [INR] of 1). The patient's non-contrast computed tomography of the brain was unremarkable for any acute hemorrhage. The patient was within the 3-hour window for the use of a thrombolytic agent. The neurology "stroke team" evaluated the patient for administration of alteplase (Activase®).

What is the fibrinolytic system and the mechanism of action of tissue plasminogen activator (t-PA)?

The endogenous fibrinolytic system utilizes the enzyme plasmin to dissolve fibrin clots. Plasmin lyses fibrin clots at various locations along their length resulting in fibrin degradation fragments that are eventually cleared by both the liver and kidney. Plasminogen, the precursor to plasmin, is a proenzyme that lacks the ability to degrade fibrin clots, but it is incorporated within the fibrin meshwork. Both endogenous urokinase and tissue plasminogen activator (t-PA) convert plasminogen to plasmin. t-PA is slowly released from damaged endothelium and eventually leads to dissolution of the clot. This can be seen in Figure 1.

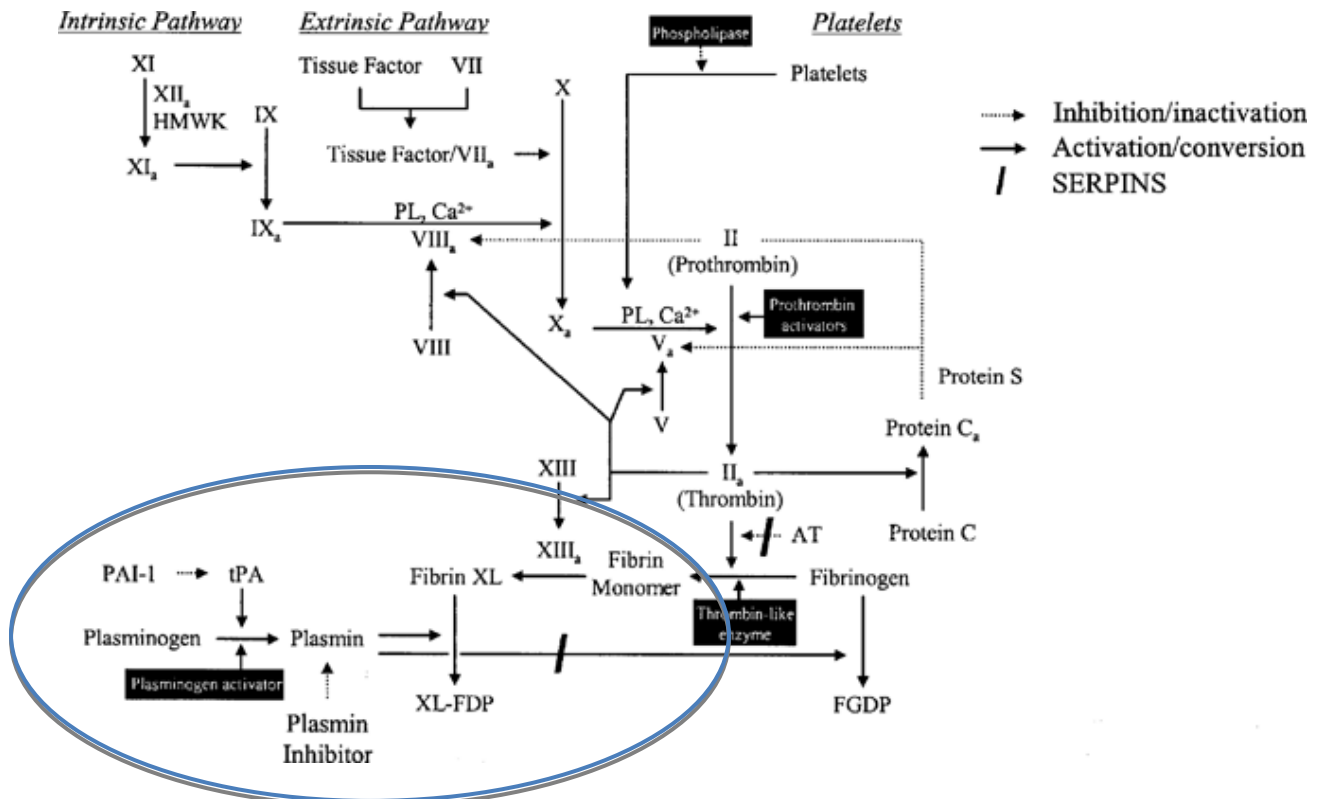


Figure 1: adapted from Goldfrank's Toxicologic Emergencies, 8th Edition (XL = cross linked; FDP = fibrin degradation products)

What are some roles of fibrinolytic agents and indications?

Thrombolytic agents are used for a variety of conditions that include acute myocardial infarction, thromboembolic disease, and cerebral vascular accident. The ideal thrombolytic would have a rapid onset of action, be fibrin-specific, carry minimum risk for bleeding complications, and be reversible in cases in which therapy is deemed inappropriate. Streptokinase, the first widely used fibrinolytic, is a protein that is secreted by several species of streptococci, that carries a relatively high risk of severe allergic reactions. There are currently three fibrin-specific thrombolytics, known as recombinant tissue plasminogen activators (rt-PA), available in the United States: These include alteplase (Activase), reteplase (Retavase), and tenecteplase (TNKase). These available agents differ in regards to their potency, resistance to inactivation by plasminogen activator inhibitor (PAI-I), and specificity to fibrin.

Case Continuation:

Despite some minor improvement in the patient's motor weakness, the patient clearly had difficulty with speech and the neurologist noted an ophthalmoplegia as well. The decision was therefore made to administer alteplase at the standard dose of 0.9 mg/kg with 10% given over a minute and the rest over 60 minutes. However, within 30 minutes of receiving the full dose of alteplase, the patient developed precipitous neurological worsening.

What are some adverse effects with the use of thrombolytics?

The most consequential adverse effect of the use of thrombolytics is bleeding, in particular intracranial hemorrhage. The incidence of intracranial hemorrhage is similar regardless of the thrombolytic used, with a rate of less than 1%. The incidence of other hemorrhage requiring transfusion is higher with a reported incidence between 5-8%. Given the potential for life-threatening bleeding, there are many contraindications as well as warnings involving the use of these potent agents. Some common contraindications include any history of prior intracranial bleeding, known intracranial neoplasm, and active internal bleeding. An age greater than 75 is also associated with an increased risk of bleeding.

Case Continuation:

The patient became progressively more confused and now demonstrated new left-sided weakness. He immediately underwent a repeat CT of the brain that can be seen in Figure 2. The patient also underwent immediate endotracheal intubation and the neurosurgical service was contacted. At this time the medical toxicology and hematology services were also contacted regarding a possible reversal agent for alteplase.

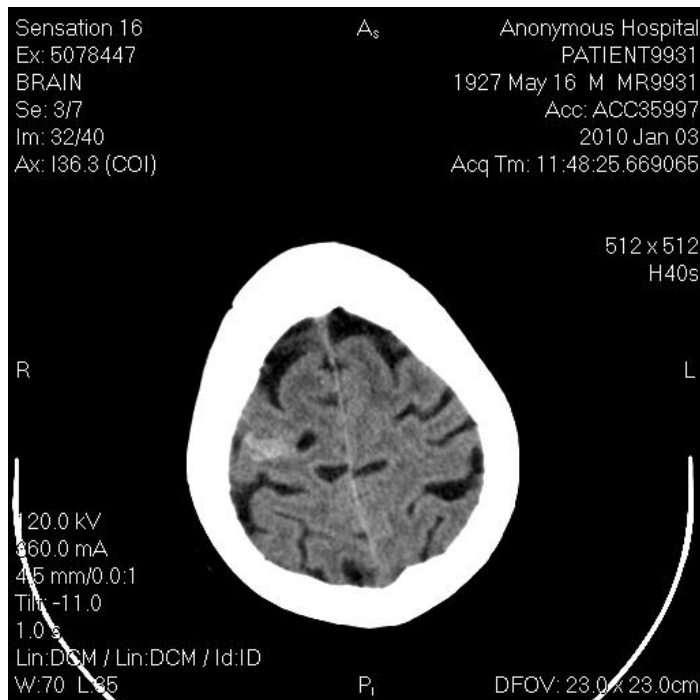


Figure 2: A repeat CT brain reveals a right frontal hemorrhage

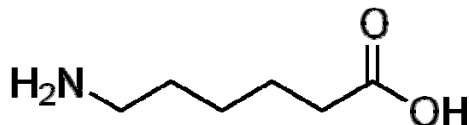
What is the management of thrombolytic-related bleeding complications?

In the event of minor bleeding secondary to thrombolytic use, supportive care is generally sufficient. Patients who develop life-threatening bleeding (i.e. intracranial hemorrhage) typically require aggressive use of blood products. The infusion of the thrombolytic (i.e. alteplase is infused over an hour) should be immediately discontinued once a suspected life-threatening

bleeding event is suspected; this includes a sudden deterioration in mental status. Many complications are not recognized until after the infusion has been completed.

Platelets should be infused for patients who use aspirin. Fresh frozen plasma (FFP) contains components of the coagulation, fibrinolytic, and complement system. FFP is indicated in the setting of factor deficiencies, massive blood transfusion, and acquired coagulopathy such as warfarin. The role of FFP is not clear with thrombolytic-related bleeding complications. Direct plasminogen inhibitors are another conceptually attractive therapy.

What are direct plasminogen inhibitors and what was their role in this case?



Aminocaproic acid

Aminocaproic acid, also known as Amicar, is an analog of the amino acid lysine. Aminocaproic acid reversibly binds to plasminogen thereby preventing its conversion to plasmin. Aminocaproic acid is primarily used to treat excessive post-operative bleeding, as occurs following liver transplantation.

Aminocaproic acid is available for oral administration (0.25 g/mL of aminocaproic acid with methylparaben 0.20%, propylparaben 0.05%, edetate disodium 0.30%). Each tablet is available as a 500 mg or 1000 mg preparation. It is also available as an intravenous formulation 5 g/20 mL (250 mg/mL).

The recommended dosing for the treatment of acute bleeding due to elevated fibrinolytic activity is 4-5 grams during the first hour of treatment, followed by a continuous infusion at the rate of 1 gm/hour. This is typically continued for about 8 hours or until the bleeding has been controlled. While the use of aminocaproic acid has theoretical benefit in the setting of tissue plasminogen activator-induced bleeds, the action of thrombolytics is typically complete by the time aminocaproic acid is administered.

Aminocaproic acid is generally well-tolerated with common adverse reactions that include nausea, emesis, headache, and myalgia. Perhaps the most feared complication regarding the use of aminocaproic acid is ischemia secondary to hypercoagulability. However, there is no definite evidence that administration of aminocaproic acid results in intravascular clotting; although only case reports support this concern it should not be dismissed.

Another related drug with a similar mechanism of action was aprotinin (Trasylo1). This drug was used for excessive post-operative bleeding, particularly in cardiac surgery. Despite the initial apparent success, concerns of safety, including a high rate of anaphylaxis, thrombosis, and mortality led, in 2007, to its withdrawal.

Case Conclusion:

Upon discussion with both the hematology and toxicology service, the patient was given 4 units of platelets as well as 4 units of fresh frozen plasma. The patient also received aminocaproic acid, 4 grams over the first hour and then 1 gram/hour for 8 hours. Another cranial CT showed extension of the hemorrhage (See Figure 3 below) after which an

intracerebroventricular shunt was placed. Despite maximal supportive care, the patient was made comfort-measures-only, given the poor prognosis, and expired 24 hours later.

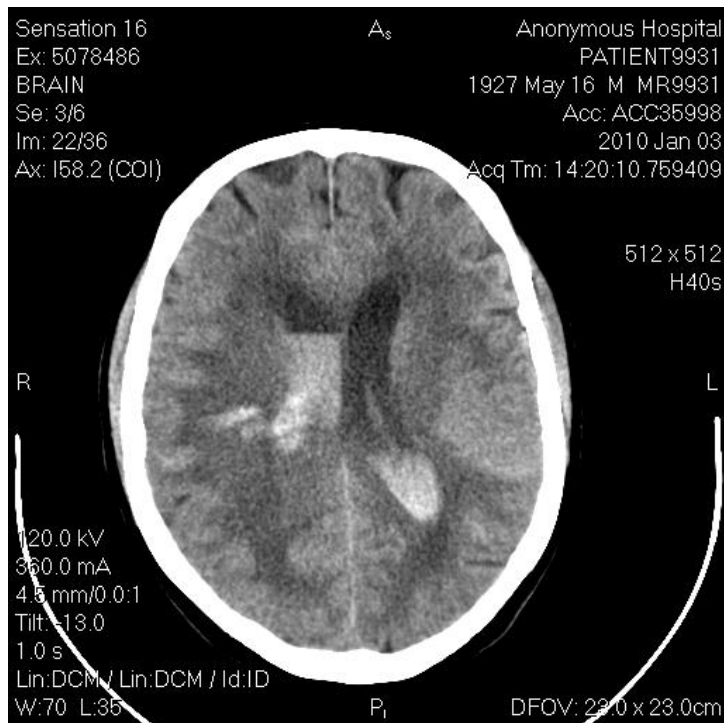


Figure 3: Another CT brain reveals worsening hemorrhage with extension into the intraventricular system and midline shift

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