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Alteplase: The Clot Buster

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**Alteplase: The Clot-Buster**

**Mayer Goldberg**

**Introduction:**

The human body is defined by many complex and inconsistent characteristics. For example, the body forms blood clots in traumatic events, but blood clots are likewise associated with hazardous or fatal conditions. Platelets are small cells, derived from the precursor megakaryocytes, which are responsible for blood clotting to prevent bleeding from a ruptured blood vessel. Platelets fasten to each other and release a coagulation factor that solidifies around the ruptured area to prevent blood loss. A subordinate quantity of platelets can result in excessive bleeding. However, high platelet numbers can progress into blood clots, which may potentially be dangerous because they produce a condition known as thrombosis. Thrombosis precedes harmful conditions such as stroke, myocardial infarction, pulmonary embolism, and other conditions associated with the disruption of circulatory blood flow.

Depending on the severity of the condition, there are different treatments available for thrombosis. Some patients may require surgery for an illness caused by thrombosis. In other instances, there are thrombolytic or fibrinolytic drugs that can be used as medicinal therapy to dissolve blood clots. Thrombolytic drugs disintegrate blood clots by converting plasminogen into plasmin. The plasmin, a serine protease, actually does the blood clot dissolving. The most important thrombolytic drug categories include tissue plasminogen activator and streptokinase (Klabunde 2005). While there are two significant families of thrombolytic medications that can be utilized in thrombolytic therapy, alteplase, a recombinant tissue plasminogen activator, is the preferred medication for treatment of acute ischemic stroke, myocardial infarction with ST elevation, and, in some rare cases, pulmonary embolism.

**Discussion:**

**Thrombolytic Therapy for Stroke**

For approximately a decade, stroke has been the third leading cause of death in the United States following cardiac diseases and cancer. Roughly 137,000 Americans die from stroke every year (Center for Disease Control 2009). Since stroke can cause brain cell damage or cell death, patients often exhibit sudden numbness or paralysis of the face, legs, or arms. Thus, stroke is the primary cause of permanent disabilities. There are two general classifications of stroke: ischemic strokes and hemorrhagic strokes.

**Ischemic Strokes**

Almost 90% of strokes are ischemic strokes, caused by decreased blood flow to the brain (Swanson 1998b). Whenever normal blood flow to the brain is interrupted, the neurons begin to die within minutes. Since brain cells require oxygen for survival, and they acquire oxygen from red blood cells, they begin to decline in function (see figure 1). There are two subcategories of ischemic strokes: thrombotic and embolic. A thrombotic stroke is caused by the formation of a blockage, thrombus, in one of the arteries supplying the brain with blood. A thrombus forms from arteriosclerosis, which is created by an accumulation of fatty deposits. An embolic stroke occurs when the body carries a blood clot from an alternate origination to a blood vessel in the brain. For example, atrial fibrillation in one of the two upper chambers in the heart can proceed to the formation of a blood clot that will travel elsewhere in the body. Thrombolytic drugs are utilized in ischemic strokes to bust open the thrombus or embolus.
the 1980s, the first drug developed for the treatment of stroke was streptokinase, but this medication was abandoned after it caused unacceptable incidence of cerebral hemorrhage (Saver and Lutsep 1995). Alteplase was developed, and research found it to be a safer and more efficient choice for thrombolytic therapy in ischemic stroke patients. An alternate study showed the efficacy of alteplase administered to acute ischemic stroke patients up to four hours after the onset of symptoms.

Figure 1: Ischemic Stroke: The illustration shows how an ischemic stroke can occur in the brain. If a blood clot breaks away from plaque buildup in a carotid (neck) artery, it can travel to and lodge in an artery in the brain. The clot can block blood flow to part of the brain, causing brain tissue death.

Patients were admitted or excluded from the alteplase clinical trial based on various elements. Some of the inclusion criteria for the acute ischemic stroke trial were the ability to have the study drug administered between 3 and 4.5 hours after the onset of stroke symptoms and the presence of stroke symptoms for at least 30 minutes with no significant improvement. Some rejection criteria were intracranial hemorrhage, seizures at the onset of stroke, and serious head injury within the previous three months. For a complete list of selective and dismissive criteria see table 1 (Hacke et al. 2008).

A total of 821 patients enrolled in the trial and were randomly assigned to either the alteplase group or a placebo group. The alteplase group had 418 patients, and the placebo group had 403 patients. Approximately 82 patients were administered the drug or a placebo between 3 and 3.5 hours, 384 patients obtained it between 3.5 and 4 hours, and 322 received it between 4 and 4.5 hours. Of the remaining patients, treatment time for 12 patients from the alteplase group and 15 patients from the placebo group were not obtainable. Additionally, one patient from the alteplase group and five patients from the placebo group were administered treatment after 4.5 hours. The trial result was a ratio of 41.6% to 36.7% in favor of the alteplase group. Although the results indicated more symptomatic intracranial hemorrhage
in the alteplase group than in the placebo group, the overall outcome of the trial showed a more favorable result for the alteplase group in the 4.5 hours range. This indicates that supplying alteplase intravenously can clinically better the condition of ischemic stroke patients up until 4.5 hours following the incipience of symptoms (Hacke et al. 2008).

**Hemorrhagic Strokes**

Hemorrhagic strokes take place following a rupture or leak from a blood vessel in the brain (Figure 2). There are two subdivisions of hemorrhagic strokes: intracerebral hemorrhage and subarachnoid hemorrhage (Swanson 1998a). In an intracerebral hemorrhagic stroke, a blood vessel bursts causing blood seepage into brain tissue. The sudden increase in pressure within the brain can cause cellular damage. Furthermore, the brain cells beyond the ruptured blood vessel are damaged due to the interruption of blood flow and oxygen delivery. A subarachnoid hemorrhagic stroke is caused by leakage from a blood vessel into the space between the surface of the skull and the brain. Hemorrhagic strokes are not treated with thrombolytic therapy because of the major risk of further hemorrhaging.

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Table 1: Major exclusion and inclusion criteria.

<table>
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<th>Main inclusion criteria</th>
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<tbody>
<tr>
<td>Acute ischemic stroke</td>
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<tr>
<td>Age, 18 to 80 years</td>
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<tr>
<td>Onset of stroke symptoms 3 to 4.5 hours before initiation of study drug administration</td>
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<tr>
<td>Stroke symptoms present for at least 30 minutes with no significant improvement before treatment</td>
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<table>
<thead>
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<th>Main exclusion criteria</th>
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<tbody>
<tr>
<td>Intracranial hemorrhage</td>
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<tr>
<td>Time of symptom onset unknown</td>
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<tr>
<td>Symptoms rapidly improving or only minor before start of infusion</td>
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<td>Severe stroke as assessed clinically (e.g., NIHSS score &gt;25) or by appropriate imaging techniques*</td>
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<tr>
<td>Seizure at the onset of stroke</td>
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<tr>
<td>Stroke or serious head trauma within the previous 3 months</td>
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<tr>
<td>Combination of previous stroke and diabetes mellitus</td>
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<td>Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range</td>
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<td>Platelet count of less than 100,000 per cubic millimeter</td>
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<td>Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or invasive treatment (intravenous medication) necessary to reduce blood pressure to these limits</td>
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<tr>
<td>Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter</td>
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<tr>
<td>Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal</td>
</tr>
<tr>
<td>Oral anticoagulant treatment</td>
</tr>
<tr>
<td>Major surgery or severe trauma within the previous 3 months</td>
</tr>
<tr>
<td>Other major disorders associated with an increased risk of bleeding</td>
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* A severe stroke as assessed by imaging was defined as a stroke involving more than one third of the middle cerebral-artery territory. NIHSS denotes National Institutes of Health Stroke Scale in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.

Source: Hacke et al. 2008
Figure 2: Hemorrhagic Stroke: The illustration shows how a hemorrhagic stroke can occur in the brain. An aneurysm in a cerebral artery breaks open, which causes bleeding in the brain. The pressure of the blood causes brain tissue death.

THROMBOLYTIC THERAPY FOR MYOCARDIAL INFARCTION

Major heart disease is the leading cause of death in the United States. According to the CDC, nearly 48% of all deaths reported in 2010 were cardiac related. Heart attack, also known as acute myocardial infarction, happens when there is an interruption of the blood

Figure 3: Heart with Muscle Damage and a Blocked Artery: Figure A shows a heart with dead heart muscle caused by a heart attack. Figure B is a cross-section of a coronary artery with plaque buildup and a blood clot.
flow to the heart, causing the cardiac muscles to die (Pub Med Health 2010a). Many heart attacks are caused by blood clots forming an obstruction in one of the coronary arteries, which carries blood and oxygen to the heart tissues. The blockage disrupts the oxygen flow to heart tissues, causing heart muscle cell death (Figure 3). Atherosclerosis, a principle cause of blockages, is the accretion of plaque that adheres to the coronary artery walls and forms an occlusion. The plaque may tear, and blood platelets may fasten to it forming a thrombus (Pub Med Health 2010a). A myocardial infarction (MI) can be classified as a non-ST elevation MI or an ST elevation MI based on electrocardiogram changes (Cleveland Clinic 2009).

**Myocardial Infarction with Non-ST Segment Elevation**

A non-ST elevation MI does not exhibit changes on an electrocardiogram. Additionally, the extent of damage is minimal since the artery is only partially obstructed (Cleveland Clinic 2009). According to the American Heart Association, there is a close correlation between non-ST elevation MI and unstable angina. Unstable angina is a condition caused by a diminished supply of blood flow and oxygen to the heart; as research indicates, it can be an introduction to a heart attack (Pub Med Health 2010b). Non-ST elevation MI and unstable angina are treated by anti-platelet agents, anti-thrombin agents, or anti-ischemic agents (Jevon et al. 2008). Although the treatments for non-ST elevation myocardial infarction and unstable angina are similar, there is a different course of action taken for a myocardial infarction with ST elevation.

**Myocardial Infarction with ST Segment Elevation**

An ST-elevation MI is caused by the prolonged obstruction of blood supply that affects a large portion of the heart. Thus, ST segment changes on an electrocardiogram are clearly visible and are easily detected (Cleveland Clinic 2009). If ST-elevation MI is detected early enough, thrombolytic treatment can be an essential part in its treatment as thrombolytics restore blood flow, thus decreasing casualties. Thrombolytic treatment is the preferred treatment for ST segment myocardial infarction, because it is the most effective at achieving reperfusion. Thrombolytic treatment can effectively restore blood flow when administered within 12 hours of symptom onset, but maximum benefit is obtained when administered promptly (Hilleman et al. 2007).

The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, known as the Gusto-I trial, was conducted to compare the efficacy of streptokinase and alteplase in ST segment myocardial infarction. Additionally, the study determined whether earlier and sustained reperfusion with alteplase improves the survival rate in people with acute myocardial infarction. A total of 41,021 patients within six hours of the onset of acute myocardial infarction with ST segmentation were randomly assigned to one of four thrombolytic treatments: streptokinase, streptokinase with intravenous heparin, accelerated tissue plasminogen activator, or tissue plasminogen activator with intravenous heparin. The primary follow-up and end point of the trial was 30 days (Hacke et al. 2008).

After the 30 days, the results indicated that patients receiving accelerated tissue plasminogen activator had a more significant reduction in mortality during the 30-day period than those administered streptokinase and any other combined strategies. There was, however, an increase of hemorrhagic stroke episodes in accelerated tissue plasminogen activator patients above the others. Still, the overall endpoint of death or permanent disability was lower in patients administered accelerated tissue plasminogen activator than in patients administered any other combination. A Gusto-III trial was soon established to determine if
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reteplase, a newer recombinant tissue plasminogen activator, was better than alteplase. More than 15,000 patients, all within six hours of the onset of symptoms, entered the trial. The 30-day mortality rate for reteplase did not exhibit any additional survival benefits in acute myocardial infarction (Hacke et al. 2008).

THROMBOLYTIC THERAPY FOR PULMONARY EMBOLISM

A pulmonary embolism is an occluded artery that disrupts the blood flow to the lungs. Deep vein thrombosis, the most common cause of pulmonary embolism, occurs when an embolus that originated in a deep thigh vein travels up to the lungs and blocks the blood flow (Fischbein 1981). Pulmonary embolism is an extremely dangerous condition, since it may cause damage to lung tissue due to a diminished oxygen supply. Additionally, it can damage other organs due to a lack of oxygen and, in some severe cases, may even cause death. Pulmonary embolism affects men as well as women. If the pulmonary embolism is caused by deep vein thrombosis, patients may exhibit symptoms such as swelling of the leg, pain or tenderness in the leg, or a discoloration of the skin on the affected area. Pulmonary embolism is responsible for 10% of all deaths, and an initial diagnosis is not straightforward. In fact, in 70% of all pulmonary embolism patients, it was not clinically suspected but confirmed after an autopsy (Davidson 1999) (Figure 4).

A majority of patients with pulmonary embolism are treated with anticoagulation medication. Anticoagulation therapy is beneficial in the treatment of pulmonary embolism, because it provides prophylaxis against further thromboembolic events while the body's own fibrinolytic system gradually lyses the embolus. Since dissolving the clot is the treatment for pulmonary embolism, many have wondered if thrombolytic therapy would be even more efficient as thrombolytic drugs dissolve clots more rapidly than endogeneous fibrinolytic activity can. There was a study comparing the efficacy of recombinant tissue plasminogen activator and anticoagulants in pulmonary embolism. As part of the study, 790 stable patients with pulmonary embolism were randomly assigned to either the heparin (anticoagulant) group or the alteplase (recombinant tPA) group. While 169 patients received recombinant tissue plasminogen activator, 550 patients received heparin alone. The overall 30-day mortality rate for patients administered tissue plasminogen activator compared to those receiving heparin was 4.7% to 11.1% respectively. Additionally, during the in-hospital phase, recurrence of pulmonary embolism was more frequent in patients taking heparin. In fact, the ratio of recurrence was 7.7% to 18.7% in favor of alteplase (Arcasoy and Kreit 1999).

SYNTHESIS OF THROMBOLYTIC DRUGS

ALTEPLASE

Alteplase is beneficial in thrombolytic treatment because it is easily synthesized using recombinant DNA technology. The composition of alteplase consists of a purified
glycoprotein consisting of 527 amino acids. It is synthesized using a complementary DNA from a human melanoma cell line. Alteplase is manufactured by secretion of an alteplase enzyme into a culture medium. After secretion of the enzyme, the antibiotic gentamicin is added to the culture causing fermentation. Gentamicin, however, is not present in the recombinant tissue plasminogen product. The product also undergoes lyophilization, which is the process of rapidly freezing and dehydrating in a vacuum (Genetech 2005).

**STREPTOKINASE**

On the other hand, streptokinase is a drug easily synthesized from a β-hemolytic streptococcus culture. However, there is a major drawback to using streptokinase. Most people have had a streptococcal infection at some point in their lives, so they are likely to have built up antibodies against streptococcal bacteria. Streptokinase is produced from streptococcal bacteria, so the circulating antibodies are likely to neutralize its effect on the clots (Finkel et al. 2009). Furthermore, once administered to a patient, streptokinase cannot be used again for some time due to its antigenic property. Thus, the antigenic property of streptokinase is one of the most significant detriments to the drug.

**MECHANISM OF ACTION**

**ALTEPLASE**

Alteplase has a mechanism of action that makes it fibrin specific and thus favorable for thrombolytic therapy (Figure 5). First, alteplase attaches to fibrin on the surface of a clot and initiates fibrin bound plasminogen. Then plasmin is cleaved from the plasminogen associated with the fibrin, fibrin molecules are broken apart by the plasmin, and the clot dissolves. Although alteplase has a low attraction for plasminogen in the plasma, it activates plasminogen attached to fibrin in a blood clot (Klabunde 2005). Alteplase’s fibrin selectivity is what makes it therapeutically useful. Thus, administering alteplase in low doses lyses only the wanted clot without degrading other proteins.

**STREPTOKINASE**

Streptokinase is a protein cultured from the broth of streptococci bacteria. Since streptokinase is not a protease, it contains no enzymatic activity and has a different mechanism of action than alteplase. Streptokinase forms an active complex with the plasminogen (Figure 6). The active complex activates and releases the plasmin to dissolve the clots (Klabunde 2005). However, streptokinase is not fibrin specific and, therefore, its

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**Figure 5:** (1) Recombinant t-PA (alteplase) binds to fibrin in thrombus (2) converts entrapped plasminogen to plasmin (3) that initiates local fibrinolysis.

Source: http://www.cathflo.com/images/moa.gif
associated plasmin lyses circulating and non-circulating plasminogen. Streptokinase decays the blood clot as well as important clotting factors, such as Factors V and VII (Finkel et al. 2009).

**Figure 6:** Streptokinase and its effect on the fibrinolytic system.  
Source: http://www.anzcp.org/CCP/Pharmacology/streptokinase_files/image002.gif

**Pharmacokinetics of the Thrombolytic Drugs**

Pharmacokinetics is the pharmacological research of drug movement within the body. Moreover, it studies the mechanism of absorption, span of drug impact, and chemical modifications the body experiences. On certain occasions, a drug will be administered intravenously to ensure that the distribution of medication is instantaneous and efficacious. The half-life of a medication is the moment it takes a medication to decrease to half its original potency. Consequently, half-life forecasts the length of time it will take for a drug to leave the blood plasma. Therefore, if a drug contains a relatively brief half-life, the body disposes and eliminates that drug quickly. In contrast, when a medication has a prolonged half-life it lingers in the blood plasma for an extended period of time. Thus, half-life is a good indicator for drug dosage, because it measures the length of time it takes for the body to dispose of a medication. While sometimes a short half-life is beneficial for patients, other times a long half-life is advantageous for a patient.

**Half-life of Thrombolytic Drugs**

Alteplase has an extremely brief half-life of approximately five minutes. There is an advantage and a disadvantage to the short half-life in alteplase. An advantage is that alteplase is a powerful clot busting medication that lyses only a specific clot and is eliminated from the body in a very brief time. A disadvantage of alteplase’s short half-life is the increased possibility of reocclusion (Greer 2007). In contrast, streptokinase has a much longer half-life than that of alteplase. However, the longer half-life of streptokinase also has disadvantages, since streptokinase has antigenic properties and poses the risk of other allergic reactions. Additionally, it is usually unsafe to administer streptokinase a second time within 6 months due to its highly antigenic property (Rivera-Bou and Brown 2010).

**Conclusion**

The Food and Drug Administration approved alteplase as a treatment for acute ischemic stroke on June 8, 1996. Astonishingly, to this very day, alteplase is the sole approved medication for patients suffering from ischemic stroke. Additionally, it has bumped stroke from the third leading cause of death to the fourth leading cause of death in the United States
The Gusto-I and Gusto-III trials indicate that alteplase is a more practical and powerful drug than streptokinase in patients suffering from myocardial infarction with ST segmentation. In fact, according to the American Heart Association, the ideal time to administer thrombolytic drugs is within 90 minutes after the heart attack. However, if administered up to 12 hours after the onset of symptoms, the chances of surviving and recovering are still enhanced (Health Guide 2010).

Pulmonary embolism is not an easily detected condition, but deep vein thrombosis, an equally serious condition, is detectable. The use of alteplase in acute massive pulmonary embolism has shown more efficient and steadfast results than that of anticoagulation therapy. Due to an extremely brief half-life, possibly resulting in reclosure, alteplase has come under fire. However, with the use of recombinant technology, more generations of alteplase are being synthesized and produced to enhance the already proficient drug.

**REFERENCES**


