Thrombolytics and Myocardial Infarction
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When the learner has completed this module, she/he will be able to:

1. Identify the basic cause of myocardial infarction.
2. Identify the indication for the use of thrombolytics.
3. Identify two diagnostic criteria for ST-segment elevation myocardial infarction.
4. Identify the most important factor determining survival after myocardial infarction.
5. Identify the two ways that thrombolytics work.
6. Identify how soon after symptom onset thrombolytics should be given.
7. Identify a marker for the effectiveness of thrombolytics.
8. Identify a common complication of thrombolytics.
9. Identify two absolute contraindications to the use of thrombolytics.
10. Identify three other drugs that are given along with thrombolytics.

Myocardial infarction (MI) is defined as the sudden, rapid development of myocardial necrosis. The basic cause of MI is a severe imbalance between the oxygen demand of the myocardium and the supply of oxygen. When this imbalance reaches a critical point, the affected parts of the heart will die.

Despite greater understanding of the pathogenesis of MI and improvements in preventative care, MI is still the leading cause of morbidity and mortality in the United States. Approximately 1.3 million Americans will have an MI each year and 500,000 – 700,000 of them will die.

The most common cause of MI is coronary artery narrowing caused by the sudden rupture of an atherosclerotic plaque. When these plaques rupture, a thrombus is formed that occludes the coronary vessel and interrupts oxygen flow.

Key Point: The myocardium cannot tolerate complete occlusion of a coronary vessel for more than four to six hours. If coronary circulation is not restored within that time, irreversible necrosis will result. Irreversible myocardial necrosis can occur within 20 to 60 minutes after a coronary artery occlusion.

But although MI is still the number one cause of mortality in the United States, there have been big improvements in care and survival rates after MI. It was clearly established that if the occluded coronary artery could be opened quickly, heart muscle could be saved. Two treatments – percutaneous coronary intervention (PCI) with angioplasty and/or stenting, and thrombolytic drugs – were developed that could rapidly and safely break down thrombi in the coronary arteries. The timely use of thrombolytic agents (also called fibrinolytics) has been proven to significantly decrease the mortality rate associated with acute MI and to decrease the incidence of the complications associated with MI.

WHAT ARE THROMBOLYTICS?

The thrombolytics are a group of drugs that are used to treat patients who are having a documented ST-segment elevation myocardial infarction (STEMI).

Key Point: A STEMI is defined as: ischemic discomfort at rest lasting > 20 minutes that is accompanied with ST segment elevation of > 0.1 mv in at least two contiguous limb leads, or ST segment elevation > 0.2 mv in at least two precordial leads, or the development of a left bundle branch block.

The thrombolytics work in two ways. They act to remove the thrombus that is causing myocardial ischemia – restoring coronary circulation – and they can prevent the formation of new clots. The thrombolytic drugs that are most commonly used to treat STEMI are streptokinase (Streptase®), alteplase (Activase®) which is also commonly called tPA , reteplase (Retavase®), tenecteplase (TNKase®) and anistreplase (Eminase®). These drugs differ is dosing, application, risks and benefits, effectiveness, etc. but they all work using the same mechanism:

Basically, the thrombolytics are plasminogen activators. Plasminogen is a naturally occurring proenzyme that is involved in clot lysis (Note: Clots are formed in the circulation all the time and are

constantly being dissolved). When plasminogen is activated (by a drug or by the normal clot lysing mechanism), it is converted into plasmin. Plasmin is a proteolytic enzyme that breaks down the fibrin and fibrinogen components of a thrombus, and degrades other components of the coagulation process, prothrombin and factors V and VII.

Although all of these drugs are approved for treating STEMI, streptokinase is seldom used in the United States. It is effective but its use is associated with a high rate of adverse effects such as anaphylaxis, allergic reactions, fever, and hypotension. In addition, as it is antigenic it cannot be given again within six months after an application.

ARE THE THROMBOLYTIC DRUGS EFFECTIVE FOR TREATING STEMI?

A large amount of clinical experience has clearly shown that thrombolytic therapy can be very effective and is relatively safe. The thrombolytic drugs have been shown to reduce mortality from STEMI by as much as 30% when they are administered within six hours from the time of the onset of symptoms. The longer the period time between the onset of symptoms and the administration of thrombolytics the less helpful they will be.

HOW ARE THROMBOLYTICS ADMINISTERED?

Thrombolytic drugs are given intravenously, and they should be given as soon as possible after the patient develops the signs and symptoms of STEMI; the sooner they are given the better. The American College of Cardiology and the American Heart Association recommend that in order for the thrombolytic drugs to be most effective, they should be given within 30 minutes of the patient's arrival at the hospital.

Key Point: The most important factor determining patient survival is the time it takes to reperfuse the myocardium. However, fibrinolytics can be beneficial when given up to 12 hours after the onset of symptoms. Fibrinolytics can be also be given by emergency medicals services (EMS) personnel in the field.

All of the thrombolytic drugs are effective, but streptokinase has been shown to be less effective than the others. Because of that and because of the risks associated with the drug, it would not be the first choice. Alteplase, reteplase, tenecteplase, or anistreplase can all be used, and it appears they all are essentially the same in terms of

effectiveness. They are different in the way they are administered, and some are easier to use than others. All patients, prior to the administration of a thrombolytic, should be placed on a cardiac monitor. A complete blood count, serum electrolytes, serum BUN and creatinine, INR, PT/PTT, and a troponin level should all be obtained. Alteplase is a commonly used thrombolytic, and is dosed using one of two regimens:

- Accelerated infusion: Patients weighing ≤ 67 kg should receive a 15mg IV bolus. This is followed by an IV infusion over 30 minutes of 0.75 mg/kg (not to exceed 50 mg), followed by an IV infusion over 60 minutes of 0.5 mg/kg (not to exceeed 35 mg). Patients > 67 kg: 15 mg IV bolus, then 50 mg IV infusion over 30 minutes, then 35 mg IV infusion over 60 minutes.

- 3-hour infusion: 60 mg (6-10 mg s bolus) IV infusion over 60 minutes, 20 mg IV infusion over 60 minutes, then 20 mg IV infusion over 60 minutes. Dose adjustments for patients < 65 kg: total dose is 1.25 mg/kg. given over three hours as described above.

WHAT OTHER DRUGS SHOULD BE GIVEN WITH THROMBOLYTICS?

The primary goal of treating a patient with a STEMI in the first few hours is to open the occluded artery and reperfuse the myocardium. The thrombolytic drugs can accomplish that, but there are other important treatment goals, as well, and there are drugs that are commonly given along with the thrombolytics. These goals are:

- Treating the patient's pain: Intravenous nitroglycerin increases blood flow to the heart and decreases preload, and is very effective for relieving the pain caused by a STEMI. Intravenous morphine is a powerful analgesic and it can also decrease preload.

- Preventing new clots from forming: It has become standard procedure to give aspirin (162 mg or 325 mg) to patients who are having a STEMI and are receiving thrombolytics therapy. Aspirin prevents platelet accumulation, which is a significant part of thrombus formation. Aspirin has been proven to reduce mortality by a significant amount and improve patient outcome in these cases. Heparin or low molecular weight heparin is also recommended; it is not clear at this poit which drug is the better choice. Clopidogrel (Plavix®) also acts to inhibit platelet

accumulation, and it definitely decreases the mortality rate , the rate of stroke, and the rate of re-infarction in patients having a STEMI.

Key Point: The aspirin should be chewed.

- Preventing re-infarction and other complications: The patient who is having a STEMI has a significant degree of coronary artery disease. In order to increase survival after the first few hours of a STEMI, beta-blockers (e.g., metoprolol), or calcium channel blockers (e.g., verapamil), and angiotension-converting enzyme (ACE) inhibitors (e.g., lisinopril) should be used within the first 24 hours. These drugs lower blood pressure, decrease cardiac oxygen demand and consumption, and using them definitely increases survival rates.

WHAT ARE THE CONTRAINDICATIONS FOR USING THROMBOLYTICS?

Thrombolytics are generally safe; complications associated with bleeding are the biggest problem. About 11% of all patients who receive thrombolytics have moderate bleeding, and approximately 0.3% - 1.3% will develop an intracranial hemorrhage.
Absolute contraindications to the use of thrombolytics include:

- Prior intracranial hemorrhage.
- Vascular lesions.
- Brain tumor.
- Ischemic stroke within two to three months.
- Recent cranial surgery or trauma.
- Active bleeding (except for normal menstrual bleeding).
- Severe, uncontrolled hypertension.

There are also relative contraindications to the use of thrombolytics:

- Ischemic stroke > three months prior.
- Pregnancy
- Major surgery ≤ three weeks prior.
- Prolonged/traumatic CPR ≤ three weeks prior.
- Internal bleeding within two to four weeks.
- Active peptic ulcer.
- Current use of anticoagulant drugs.

ARE THROMBOLYTICS A BETTER CHOICE THAN PERCUTANEOUS CORONARY INTERVENTION?

The majority opinion at this point is that PCI is superior to thrombolytics for treating an STEMI. However, the majority of hospitals in the United States do not have cardiac catheterization laboratory and staff. Patients suffering an STEMI could be transferred to a facility with a cardiac catheterization laboratory, but PCI is most effective if the time from the onset of symptoms to catheterization is < 90 minutes. Making the transfer in that period of time often isn't possible.

HOW CAN THE CLINICIAN KNOW WHEN THE THROMBOLYTICS ARE WORKING?

The goal of thrombolytic therapy is to restore perfusion to the affected area of the myocardium. Unless the clinician has access to a cardiac catherterization laboratory, he/she will have to depend on indirect markers to determine if the ischemic area of the heart has been reperfused and the therapy has been successful.

Decrease in and/or resolution of ST segment elevation appears to be a reliable indirect marker for the success of thrombolytic therapy. If the ST segment elevation has decreased by ≥ 50%, this is associated with a higher rate of coronary artery reperfusion. The available research has clearly shown that the more the ST segment is decreased, the greater the improvement in mortality rates. Other indirect markers of reperfusion such as the presence/absence of chest pain, myoglobin levels don't appear to be very sensitive or reliable.

WHY DON'T THROMBOLYTIC DRUGS WORK?

Thrombolytis don't always work, and in some case, they only work temporarily. In about 50% to 80% of all patients, the thrombolytics produce a significant increase in coronary artery blood flow. But fibrinolytic therapy can fail to lyse a clot or the original clot can be dissolved but a new one can form.

No one is quite sure why the thrombolytics drugs fail; there are probably multiple reasons. It may be that there is not enough circulation to the ischemic area to deliver an adequate quantity of the drug. It may be that there are subtle changes in the formation and/or components of the clot, or the age of the clot may be a factor. The damage to the vessel wall caused by plaque rupture may be important. Formation of a new thrombus may actually be caused by lysis of the original clot.

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