

THROMBOLYTICS

PURPOSE

To familiarize and acquaint the transfer Paramedic with the skills and knowledge necessary to adequately maintain thrombolytic agents and their adjunctive treatments in the interfacility transfer environment.

OBJECTIVES

COGNITIVE

- Discuss the purpose of thrombolytic therapy
- List the five types of thrombolytic agents with their respective dosages
- List the potential side effects of thrombolytic therapy
- Explain the purpose of the five adjunctive pharmacologic agents during thrombolytic therapy
- Describe the proper methods for administering the five thrombolytic agents
- Identify the proper dosage and potential side effects of the seven adjunctive pharmacologic agents during thrombolytic therapy
- Describe the pathophysiology involved in an acute myocardial infarction
- Recall that thrombolytic agents may be used for other thrombic emergencies
- State the sequential management to handle bleeding problems

PSYCHOMOTOR

- View various 12 lead ECG recordings of acute infarctions

AFFECTIVE

- Explain the importance of handling a thrombolytic patient gently
- Explain the rationale for dividing the contraindications to thrombolytics into potential and absolute
- Defend the reasons for adjunctive pharmacologic therapy

OVERVIEW

With approximately 1.5 million Americans experiencing heart attacks each year, it is easy to see why coronary artery disease is the United States' number one cause of death. Over half-a-million people will die before they reach the hospital.

Thrombolytics were first used in the late 1950's, but it was not until nearly 30 years later that they became the standard in treating myocardial infarctions (MI). There are presently five agents in use today.

Streptokinase (SK) was the original thrombolytic with Anisoylated Plasminogen SK Activator Complex (APSAC) developing later as a SK hybrid. Due to the manufacturing process these agents should not be used if the patient has previously been treated with them in the past six months. Additionally, a history of a recent "strep" infection may preclude their use.

Tissue plasminogen activator (tPA, Alteplase) has the distinction of being considered a clot specific agent at low doses. This implies that tPA will work on those clots in the coronary arteries that were recently formed and leave other clots in the systemic circulation alone. Unfortunately, at therapeutic levels, tPA does not appear to noticeably decrease the incidence of bleeding when compared either with SK or Urokinase (UK).

The newest agent, Retavase, was approved by the Food and Drug Administration in the latter part of 1996. This thrombolytic is given as a double bolus of 10 Units each with the second bolus given 30 minutes after the first. Paramedics in Lansing, MI and Miami, FL are currently in prehospital field trials with this thrombolytic agent.

The last agent, Urokinase (UK), has been involved in the least amount of trials. UK has been available for use a longer period of time than either tPA or APSAC.

The purpose of thrombolytics is the "lysing" or destruction of the thrombi which has precipitated the heart attack, stroke, or pulmonary embolism. The five brands of thrombolytics all, either directly or indirectly, activate plasminogen which is the precursor to plasmin. The plasmin then destroys the fibrin surrounding the clot. Once the thrombus has been dissolved, reocclusion may occur unless other pharmacologic agents are present. These agents will be discussed in a later section.

PATHOPHYSIOLOGY

The events which precede the occlusion of a coronary vessel occur in a very predictable and straightforward manner. The first step is that an event has occurred that has damaged the delicate endothelial lining, tunica intima, of the blood vessel. Once this has occurred the clotting mechanism begins.

Platelets adhere to the rough edges of the damaged vessel wall and rupture. This rupturing releases serotonin (which causes localized vasoconstriction), adenosine diphosphate (ADP) and thromboxanes. ADP promotes the attraction of additional platelets to the damaged site as well as thromboxanes (a type of prostaglandin), which causes further aggregation and clotting. This is the reason that aspirin, which inhibits prostaglandins, is such an important component in the treatment of an acute myocardial infarction (AMI). Prothrombin, a naturally occurring substance in the body, is converted into its active form thrombin. The enzyme thrombin then acts on fibrinogen, which is manufactured in the liver, to transform the fibrinogen into fibrin. Fibrin acts like a net to secure the clot in place.

From this point, unless the body's own naturally occurring fibrinolytic (plasmin) can dissolve the clot, or definitive treatment (thrombolytics) takes place, the cycle keeps building on itself, with the help of fatty acids (plasma cholesterol), until the blood vessel becomes occluded. Once the vessel has become occluded, or if perfusion distal to the thrombus is reduced sufficiently, the patient experiences a heart attack and damage results to the myocardium.

TRANSPORT CONSIDERATIONS

As the patient reperfuses they will oftentimes experience "reperfusion arrhythmias". These arrhythmias are usually bradycardic, short lived and usually do not require any aggressive interventions. In 1991, a study published in the Heart & Lung journal found that dysrhythmias began in 80 % of the cases within 1.5 hours from onset of thrombolytic therapy.

TYPES OF THROMBOLYTICS

ALTEPLASE

Trade Name:

Activase

Onset:

Immediate

Peak:

45 minutes

Duration:

4 hours

Dosage:

100 mg IV over 3 hours, given as: 60 mg in the first hour (6-10 mg of which is bolused first over 1-2 minutes) the remaining 40 mg is infused at 20 mg/hr.

ANISTREPLASE

Trade name:

Eminase

Onset:

Immediate

Peak:

45 minutes

Duration:

6 hours to 2 days

Dosage:

30 units IV over 2 to 5 minutes

STREPTOKINASE

Trade name:

Streptase, Kabikinase

Onset:

Immediate

Peak:

20 minutes to 2 hours

Duration:

4 hours

Dosage:

140,000 units followed by maintenance infusion. Loading dose is 20,000 units with maintenance infusion of 2,000 IU/min over 1 hour.

Note: Due to manufacturing process a chance for an allergic reaction is possible

UROKINASE

Trade name:

Abbokinase

Onset:

Immediate

Peak:

20 minutes to 2 hours

Duration:

4 hours

Dosage:

6,000 IU/minute is initiated for up to 2 hours. Typical dose is 500,000 IU total.

RETEPLASE, RECOMBINANT

Trade Name:

Retavase

Onset:

Unknown

Peak:

Unknown

Duration:

Half life is 13-16 minutes in length

Dosage:

Double bolus of 10 U + 10 U each given over 2 minutes. The second bolus is administered in 30 minutes if no untoward effects occur.

Thrombolytics may be used for other types of medical emergencies that are caused by a thrombus. Recently, the use of thrombolytics in the setting of an embolic stroke has been performed. Alteplase, streptokinase, and urokinase are approved for use in massive (hypotension) pulmonary emboli. Streptokinase and urokinase may also be used in the treatment of deep venous thrombosis (DVT) and to clear blocked IV catheters.

In the setting of excessive bleeding due to the use of thrombolytics, there is an antidote available. Aminocaproic acid (Amicar) is given 5 g PO or slow IV followed by a dose of 1.25 g every hour up to a maximum dose of 30 g total in a 24 hour period.

CONTRAINDICATIONS

POTENTIAL ABSOLUTE

- ◆ Active internal bleeding
- ◆ History of any cerebrovascular accident, intracranial neoplasm, arteriovenous malformations or aneurysm.
- ◆ Recent (within 2 months) intracranial or intraspinal surgery or trauma
- ◆ Past or present bleeding disorder
- ◆ Uncontrolled hypertension (systolic > 180 mm Hg, diastolic > 110 mm Hg)
- ◆ Pregnancy

POTENTIAL RELATIVE

- ◆ Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- ◆ Prolonged CPR (longer than 10 minutes)
- ◆ Recent (within 10 days) major surgery at non-compressible site (e.g., CABG)
- ◆ Documented cerebrovascular disease
- ◆ Recent (within 7 days) gastrointestinal or genitourinary bleeding
- ◆ Significant liver dysfunction
- ◆ PHYSICALLY advanced age (> 75 years with multiple disease states beyond AMI)
- ◆ Patients currently receiving oral anticoagulants
- ◆ Previous thrombolytic therapy
- ◆ Trauma to the head in the last two weeks?
- ◆ Surgery in the last two weeks?
- ◆ Any trauma in the last two weeks?

SIDE EFFECTS

There are numerous side effects which may occur following the administration of thrombolytic agents. With the exceptions of urticaria (due to an allergic reaction) and the effects of reperfusion, all side effects may be lumped into one category, hemorrhage. Whether it is intracranial, conjunctival, internal, etc., it is bleeding that is the major side effect. Handle these patients very gently to avoid these problems. Specifics of bleeding management will be dealt with in the next section.

BLEEDING MANAGEMENT

- ◆ Avoid IM injections
- ◆ Avoid unnecessary handling of patient
- ◆ Consider padding the side rails of the stretcher
- ◆ Keep venipunctures to an absolute minimum
- ◆ For active bleeding venipuncture sites apply direct pressure for at least 15 minutes
- ◆ Keep the involved extremity in straight alignment
- ◆ Be aware that the bleeding may be internal. Keep a close eye out for hypovolemia
- ◆ Aggressively assess the patient for signs and symptoms of internal hemorrhaging every 15 minutes for the first hour and every 30 minutes from hours two to eight of the therapy.
- ◆ Avoid placing nasotracheal tubes and nasogastric tubes.

SEQUENTIAL MANAGEMENT TO BLEEDING PROBLEMS

- ◆ Apply manual pressure to bleeding site
- ◆ Administer crystalloid volume replacement
- ◆ Interrupt anticoagulant therapy
- ◆ Interrupt thrombolytic therapy

ADJUNCTIVE AGENTS

NITROGLYCERIN

Effects:

Nitroglycerin acts as a smooth muscle relaxant which serves to decrease myocardial oxygen demand by reducing the **preload** on the left ventricle. At the same time it increases the myocardial oxygen supply by dilating the coronary vessels. Nitroglycerin acts primarily on the venous side of the systemic circulation, but at high doses does exhibit some arterial effect.

Dosage:

IV form is typically initiated at 10-20 mcg/min and titrated to effect

Contraindications:

Hypersensitivity to the agent
Hypotension

Onset:

Immediate with IV form

Side effects:

- Headache
- Orthostatic hypotension
- Tachycardia
- Flushing
- Palpitation
- Nausea/Vomiting

LIDOCAINE

Effects:

A Class I B antiarrhythmic which affects the fast channel (sodium) during depolarization. This causes a decrease in excitability and conduction, as well as, an increase in the fibrillation threshold (the point at which the heart may begin to fibrillate). Lidocaine works only on the ischemic portions of the heart. In effect, it makes those cells of the heart which are “a little sick” and irritable, very sick to the point where they will not initiate an impulse.

Dose:

1-1.5 mg/kg IV bolus (maximum of 3 mg/kg), followed by a 4:1 maintenance infusion at 2-4 mg/min.

Contraindications:

- Hypersensitivity to the agent
- Heart blocks
- Sick Sinus Syndrome

Onset:

Immediate

Side effects:

- Confusion
- Tremor
- Hypotension
- Bradycardia
- Worsened Arrhythmias

HEPARIN

Effects:

Inhibits the formation of new clots by activating antithrombin III-thrombin complex which deactivates thrombin and prevents fibrinogen from being converted to fibrin

Dosage:

Tends to be patient specific. The typical dosing may be 5,000 to 7,500 units IV bolus followed by an infusion at a rate of 1,000 units/hour. The rate is adjusted according to PTT times (partial thromboplastin times). If an overdose occurs, protamine sulfate is the antidote.

Contraindications:

- Coagulation disorders
- Ulcers
- Recent surgery
- Active bleeding
- Hypersensitivity to the agent

Onset:

Immediate

Side effects:

- Hemorrhage
- Increased clotting times

ASPIRIN

Effects:

Blocks prostaglandin formation which in turn leads to a decrease in the synthesis of thromboxane A₂. Thromboxane A₂ causes platelets to adhere to each other.

Dosage:

240 mg.

Contraindications:

- Known hypersensitivity to the drug
- Bleeding disorders
- Use with caution in patients with a known hypersensitivity to NSAIDS

Onset:

5-30 minutes after ingestion

Side effects:

Tinnitus
Dizziness
GI disorders

BETA BLOCKERS (METOPROLOL)

Effects:

Beta blockers have been demonstrated to provide a substantial decrease in myocardial ischemia and reduce the incidence of reinfarction. As their name implies, they block the beta effects on the body. Some agents, such as metoprolol, are beta₁ specific and act to decrease the rate, force and automaticity of the heart. These actions may save some of the myocardium and reduce the incidence or reperfusion arrhythmias by decreasing the myocardial oxygen demand. Due to their effect of reducing the automaticity of the myocardial cells, beta blockers also exhibit an antiarrhythmic effect.

Dosage:

Metoprolol 5 mg IV every 5 minutes for a total of three doses; then 25-50 mg PO every 6 hours.

Contraindications:

Known hypersensitivity to the drug
Heart rate <45 beats per minute
2nd or 3rd degree heart block
PR interval of .24 seconds with 1st degree block
Systolic BP <100
Moderate to severe cardiac failure

Onset:

Within 5 minutes IV

Side effects:

Fatigue
Dizziness
Bradycardia
Hypotension

MORPHINE SULFATE

Effects:

Morphine has three primary actions which benefits the patient. First, morphine is a venodilator which serves to reduce the workload of the heart. Second, morphine is a central nervous system depressant which will aid in the reduction in the amount of circulating catecholamines (catecholamines will only serve to increase the demand on the already ischemic heart). Finally, it is a potent analgesic which will aid in relaxing and calming the patient.

Dosage:

1-3 mg every 5 minutes until desired relief is obtained

Contraindications:

Known hypersensitivity
Hypotension

Onset:

Less than 5 minutes IV

Side Effects:

Respiratory Depression
Hypotension
Lightheadedness

OXYGEN

Effects:

Elevates the PaO₂ thereby increasing the amount of oxygen available for the ischemic tissue of the heart

Dosage:

American Heart Association recommends beginning with 4 L/min via nasal cannula and increasing the amount of oxygen until the oxygen saturation is greater than 97%.

Contraindications:

The problem with COPD patients and hypoxic drive is greatly overestimated. Less than 2% of the COPD patients utilize hypoxic drive. There are no contraindications to the administration of oxygen.

Onset:

Immediate

Side Effects:

None