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# Thrombolytic Therapy in Acute Myocardial Infarction

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It is estimated that 800,000 people in the U.S. suffer an acute myocardial infarction (AMI) each year; in addition, an estimated 500,000 deaths annually are attributed to AMI (1). The role of thrombolytic therapy in AMI had been vague (2) until the late 1970's and early 1980's at which time research utilizing coronary angiography during AMI showed that in approximately 86% of all cases, a clot or thrombus was present in the infarct-related artery (3). This finding renewed interest in the area of thrombolytic therapy.

Initial studies involving thrombolytic therapy were performed using streptokinase (SK) via the intracoronary route (4). These showed a 75% reperfusion rate of the occluded coronary artery if therapy was initiated within the first three hours of onset of AMI (5). However, due to limitations of the intracoronary route such as limited availability of cardiac catheterization labs, the need for specially trained staff available around the clock, and delay in treatment intrinsic to the catheterization procedure itself, more and more research turned to intravenous (IV) thrombolytic therapy. Streptokinase and urokinase (UK) were the first generation of "lytic" agents tested (6).

Subsequently, research has led to the development of new thrombolytic drugs that can be termed second generation agents. These include tissue plasminogen activator (TPA), anisoylated plasminogen streptokinase activator complex (APSAC) and pro-urokinase (Pro-UK)(6). Despite their potential for safer and more effective therapy in AMI, further study and data are needed before they completely supplant the first generation thrombolytic agents.

## CORONARY THROMBUS FORMATION

The coronary arteries, as well as other blood vessels, are normally lined by an extremely smooth and slick layer of endothelial cells called the intima. The blood normally contains substances which promote and those which inhibit blood coagulation. Normally, the balance between the two groups of substances is in favor of the anticoagulants so that obstructions do not occur in smooth and free flowing vessels.

Coronary atherosclerosis is caused by the accumulation of cholesterol and other fatty substances which form deposits beneath the intima of the coronary arteries. These deposits can cause narrowing (stenosis) with superimposed rupture, cracking or hemorrhage of the intima (2). This presents a rough surface to the bloodstream. The rough surface of the atherosclerotic lesion causes attraction of platelets. The platelets become sticky, swollen and irregular in shape and attract still more platelets in a vicious cycle to form a platelet plug. The rough surface also triggers the formation of prothrombin activator which converts prothrombin to thrombin. Thrombin then combines with fibrinogen to form fibrin threads which will become woven into the platelet plug enmeshing platelets, red blood cells and plasma to form a solid blood clot (7,8).

Acute myocardial infarction is most often related to such thrombus formation in a coronary artery. The coronary artery occlusion by the clot may occur at the site of a preexisting atherosclerotic stenosis or more distally if the clot breaks away, lodging in a narrower segment of the coronary vasculature.

## THROMBOLYSIS

Thrombolysis, the breakdown and dissolution of the fibrin and clot, occurs when plasminogen is converted to plasmin by plasminogen activator. Plasminogen is a normal part of all blood clots, trapped with the plasma during clot formation. The plasmin is a proteolytic enzyme that digests fibrin and other clotting factors to affect dissolution of the clot. The conversion of plasminogen to plasmin occurs intrinsically, but at a very slow rate (8). The thrombolytic agents accelerate the conversion of plasminogen to plasmin.

## METHODS OF ACTION FOR THROMBOLYTIC AGENTS

Each thrombolytic agent catalyzes the conversion of plasminogen to plasmin in a generally similar, yet different method. For example, SK, a non-enzymatic protein acquired from the bacteria group C beta hemolytic streptococci (2), achieves its thrombolytic action via indirect activation of plasminogen, thus converting fibrin bound as well as circulating plasminogen to plasmin (7). Plasmin then acts to lyse fibrin, the foundation of the thrombus (7). However, due to its action on circulating plasminogen and other clotting factors (V and VIII), SK causes a systemic lytic state (2). Because of this systemic lytic status, extreme caution must be employed to avoid serious and potentially life threatening hemorrhage.

Urokinase is produced in vivo by mast type cells, such as endothelial cells, and is then secreted into the bloodstream in the

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form of the pro-enzyme, pro-urokinase (7). However, in the event of an AMI, the body cannot produce sufficient amounts of UK quickly enough to effect rapid lysis of the coronary thrombosis. UK is therefore produced for commercial use from human renal cells, an expensive process (7). UK, unlike SK, acts directly with plasminogen to convert circulating and fibrin bound plasminogen to plasmin, thereby catalyzing thrombus dissolution (7).

A third and newer thrombolytic drug is tissue type plasminogen activator (TPA) which, in addition to SK, recently gained FDA approval for use in treating AMI. TPA is a somewhat more fibrin specific drug, thus its effect on circulating plasminogen is to some degree diminished. TPA is an intrinsically occurring protease, which is produced by various human tissue cells in response to certain stimuli and has the ability to directly activate plasminogen (2,5,7). Currently TPA is manufactured through the use of recombinant DNA technology (2,7). The foremost advantage TPA holds over other thrombolytic agents is its relative affinity for fibrin bound plasminogen in contrast to circulating plasminogen (7). This characteristic of TPA offers a diminished systemic lytic effect, certainly a desirable attribute.

APSAC, essentially a second generation SK, is another of the three newer thrombolytic agents and is only available for use through entry into an investigational protocol at the present time. This new drug is derived through chemically altering (acylation) the active center of the SK molecule (3,5,9). Because of its unique structure, APSAC can be given as an IV bolus injection and has a slightly increased specificity for fibrin bound plasminogen (5,9). One other benefit APSAC has is its 120 minute half-life, giving extended thrombolytic activity when compared to the half-life of other thrombolytic drugs (2,9). Once APSAC is injected into the bloodstream, it undergoes deacylation at a controlled rate. This restores its ability to activate plasminogen to form plasmin, thus effecting clot dissolution (9). Unfortunately, when APSAC is given at its therapeutic dosage for coronary thrombolysis (30 units) it also causes a systemic lytic state (5,9).

The last of the five thrombolytic agents, pro-urokinase (pro-UK) is a precursor of UK and, like TPA, is released from various cells within the body (5,7,10). It is a highly clot selective drug, though its exact mechanism of action is not known (5,7). One speculation for its mode of action is that it activates fibrin bound plasminogen as opposed to circulating plasminogen (11). Another theory is that when pro-UK is given, it is bound with an inhibitor which is dissociated by fibrin then converted to a form of UK, the plasminogen activator (11). Pro-UK is manufactured using recombinant DNA technology and is only available for investigational use.

A sixth method of thrombolysis, monoclonal antibodies, is also under investigation, though it is still in the early stages of development. This new and promising technique involves the tagging of SK or UK with fibrin specific antibodies thereby producing a very highly fibrin specific thrombolytic drug (5,7).

## GOALS OF THROMBOLYTIC THERAPY

Given early, within four hours of onset of AMI, thrombolytic therapy has, depending upon the agent given, approximately a 60-80% chance of thrombolysis (Table 1) with subsequent restoration of blood flow to the ischemic myocardium. With reperfusion, myocardium can be salvaged, thus limiting infarct size, preserving left ventricular function, and decreasing mortality both in hospital and up to one year post treatment (2). The benefits of reperfusion have been well demonstrated in the Thrombolysis in Myocardial Infarction (TIMI) trial, utilizing IV TPA (12) and in a large Italian study using IV SK in nearly 12,000 patients (13).

## PATIENT SELECTION

Regardless of which thrombolytic agent is administered, the key to a successful and uncomplicated course of treatment is adherence to a strict protocol for patient selection (14). This protocol should have criteria for both inclusion and exclusion (1). Patients should first meet criteria for inclusion (14,15):

1. Continuous chest pain of 30 minutes duration or longer, unrelieved by nitroglycerine (IV or sublingual), or sublingual nifedipine
2. ECG changes indicative of AMI, i.e. ST elevation of 0.1mV in one or more standard leads, or at least 0.2mV in one or more precordial leads
3. Patients should ideally be candidates for coronary angiography in order to more appropriately define treatment
4. Patients must be able to receive the thrombolytic drug within four hours from onset of symptoms, since after four hours the chance of reperfusion and limiting the infarct size declines sharply (2,3,5,13)

One exception to criteria number 4, however, may be with TPA which appears to have a fairly good rate of reperfusion in the four to six hour range, though the amount of myocardium salvaged may be limited.

After patients have met the inclusion criteria, they must be subjected to evaluation for exclusion criteria (14,15):

1. Age greater than 75 years (carries increased risk for cerebral hemorrhage)
2. Patients on coumadin therapy (increases risk for bleeding secondary to an already altered clotting system)
3. Patients with active internal bleeding
4. History of CVA, intracranial neoplasm, AV malformation, or cerebral aneurysm
5. History of recent (within 6 months) intracranial or intraspinal surgery

| Drug | Route/Dose | Time from onset of AMI | Avg. time to reperfusion | % reperfusion | Cost per dose |
|---|---|---|---|---|---|
| Streptokinase | IV 1,500,000 units over 60 min | < 3 hours | 30-45 min. | 55-65% | $500-$1,000 |
| TPA | IV 70 mg over 3 hrs. | < 4 hours | 30-45 min. | 70-80% | $2,500 to $4,000 |
| APSAC | IV 30 units over 3-5 min. | < 3hours | 45 min. | 65-70% | approx $1,000 |
| UK | IV 2,000,000 units in bolus | < 3 hrs. | 30-45 min. | 60-65% | $2,000 to $4,000 |
| Pro-UK | IV 70 mg. over one hour | < 3 hrs. | 30-45 min. | 65-70% | unknown (high) |

**Table 1 - Comparison of Different Thrombolytic Drugs: Dose , Effect, and Cost**

6. History of recent G.I. or G.U. surgery (within 10 days)
7. History of external chest massage (for this episode of chest pain/AMI) or any significant trauma
8. Recent history (within 6 months) of severe uncontrolled hypertension, or at any time a history of complications resulting from severe hypertension, i.e. hypertensive encephalopathy
9. Patients having undergone surgery in the previous 10 days which could result in life threatening bleeding
10. Pregnant or lactating women or women of childbearing potential (unknown consequences)
11. Patients with prosthetic valves, dilated cardiomyopathy or ventricular aneurysm (risk of breaking up chronic thrombus formation and causing emboli)
12. Patients who have received SK within the previous 6 months (if SK or APSAC are to be given for this event due to antigenicity of these two drugs)

## PATIENT MANAGEMENT

Once the diagnosis of AMI is determined and all criteria for receiving thrombolytic therapy are met, the patient must then be made to understand the treatment and its goals. After drawing blood for baseline lab work (to include CBC, chemistry profile, PT, PTT, thrombin time, platelet count, cardiac enzymes with isoenzymes, and type and crossmatch for at least 2 units of blood), thrombolytic treatment may begin. The patient must then be watched closely for any adverse events such as allergic reaction (mostly with SK and APSAC), bleeding, hypotension, severe headache and/or change in level of consciousness (16,17). Allergic reactions to SK or APSAC are infrequent but can be lessened by giving 50 mg. of diphenhydramine and 100-500 mg. of hydrocortisone IV just prior to treatment (16). Bleeding, should it occur, may necessitate stopping thrombolytic therapy and administering blood, fresh frozen plasma, or aminocaproic acid. Hypotension can occur but is usually transient and benign. Headache or changes in level of consciousness require immediate stopping of thrombolytic therapy followed by diligent monitoring of neurologic condition. In addition to observing for thrombolytic related adverse events, the patient requires close monitoring and treatment for other problems associated with AMI (i.e., hypotension associated with cardiogenic shock, dysrhythmias, and pain). The patient should also be observed closely for signs frequently associated with reperfusion in the infarct-related vessel: decrease or cessation of chest pain, rapid resolution of the ST segment elevation, or reperfusion dysrhythmias (frequently accelerated idioventricular rhythms)(16).

Once thrombolytic therapy has been initiated, the next important step for optimal patient treatment is urgent coronary angiography, in order to determine if reperfusion has occurred. If reperfusion with good flow in the infarct-related artery is present, further intervention by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) is probably not necessary immediately. Recent studies suggest that PTCA of the underlying atherosclerotic lesion can probably be done more effectively if delayed for several days. In this situation, it is essential to keep the patient

therapeutically anticoagulated with heparin (IV infusion to maintain a PTT approximately 1.5-2x control). Otherwise, the incidence of reocclusion is very high. If reperfusion with good flow has not been effected by thrombolysis, PTCA can be done immediately. CABG may be necessary after reperfusion if severe multivessel disease is present, or if the occasional single-vessel disease that cannot be adequately managed by PTCA is associated with a large area of jeopardized myocardium. Cardiac catheterization, PTCA, and even CABG can all be effected without markedly increased risk and complications by experienced angioplasters and surgeons.

## FUTURE DIRECTIONS OF THROMBOLYTIC THERAPY

At this time, treatment with thrombolytic agents in the United States is restricted to the hospital setting. However, with more and better drugs becoming available, such as TPA, and probably soon APSAC, the question of whether or not to initiate thrombolytic therapy in the prehospital setting (utilizing skilled paramedical personnel in constant communication with a base station physician) is being raised. As a result, patients would almost certainly benefit from earlier reperfusion accompanied by significant reductions in AMI related morbidity and mortality.

Indeed, the idea of administering thrombolytic therapy in the prehospital setting is not a new concept. Already, studies of this type have been carried out; one in France, and another in Jerusalem using APSAC and SK, respectively (15,18). Each of these two studies reported favorable data in regard to the safety and practicality in this method of administering thrombolytic agents (15,18).

Each study required that patients meet entry criteria nearly identical to those listed here. The major difference in the study designs were in their choice of thrombolytic agent. The French study involved administering APSAC, 30 units IV, over approximately 4 minutes. The Jerusalem group gave SK, 750,000 units, as an IV infusion over 20 - 30 minutes. Both study groups used what they termed a mobile intensive care unit (MICU) staffed with a physician, in addition to paramedical personnel (15,18).

Reports from these studies indicated that a thrombolytic drug administered in the prehospital setting can reduce the time from onset of AMI to initiation of thrombolytic therapy by approximately 60 minutes (15,18). In fact, the French group estimated from their data that by instituting treatment in the field, most patients could begin receiving a thrombolytic agent within 3 hours of onset of symptoms, and that as many as half of these patients might have treatment begun inside of 2 hours (18). Reperfusion rates for infarct related arteries where reported as 75% in the French group and 84% in the Jerusalem study. Neither group reported any severe adverse events related to the administration of either APSAC or SK in the prehospital setting. Thus, these authors further concluded that prehospital administration of either APSAC or SK can be feasible, and relatively safe (15,18).

However, despite the favorable data presented above, prehospital administration of thrombolytic drugs is not without stumbling points. Some of these include, but are not limited to, difficulty with making an accurate diagnosis, improper or inaccurate screening for inclusion and exclusion criteria, which drug is best for field use, and what level of education should personnel be required to have for adequate staffing of a MICU ambulance.

Probably the most important potential error would be making an inaccurate diagnosis. Many conditions (such as hiatal hernia, costrochondritis, gastritis, and pericarditis) can have symptoms which mimic those of AMI. Should a patient with one of the above problems be misdiagnosed as having an AMI, and then be given a thrombolytic drug, the consequences could be potentially fatal. If, however, a good set of clinical findings were known to have a high rate of accuracy for diagnosing AMI, then these could be used by the field personnel to relay useful diagnostic information to a base station physician for assistance in making a proper diagnosis. Unfortunately, there are no consistently accurate sets of clinical indicators or predictors for diagnosing AMI (19). Clinical symptoms such as chest pain, radiation of chest pain, diaphoresis, SOB, nausea and vomiting, and ST elevation on rhythm ECG strips were evaluated in varying combinations and provided accurate diagnostic assistance in only 47% to 79% of patients whose definative diagnosis was AMI (19).

On the question of proper use of inclusion and exclusion criteria, an EMS system must develop a specific protocol for AMI and thrombolysis which is strictly adhered to. Such a protocol can be derived using the various reference sources used in this and similar reviews, thrombolytic drug research protocols, and drug package inserts. This protocol could then be tested by screening suspected AMI patients in the field for thrombolytic therapy, then comparing the prehospital diagnosis with the in-hospital diagnosis to determine the proficiency by which AMI patients are detected. The prehospital accuracy rate with such a protocol may be the determining factor regarding the feasibility of prehospital thrombolytic therapy within a given location and EMS system.

The clinical skills of the personnel who staff EMS units must be considered. They must have or be capable of developing the skills to assist the on-line physician with the diagnosis of AMI and be able to competently deliver thrombolytic drugs. Since a physician is usually not present first hand in the field, it is the field personnel on whom the physicians must rely upon for information used to make the diagnosis with their remote but on-line input. The question then must be whether or not current paramedical personnel can be adequately trained to participate in diagnosis of AMI and the prehospital administration of thrombolytic agents. Or, should this level of care be left to a new classification of EMS personnel, such as a higher level para-

medic, a registered nurse skilled in emergency medical treatment or critical care, physicians assistants with training weighted towards cardiology, or some combination of these? This question will have to be answered before patients can routinely be treated with a thrombolytic drug prior to hospitalization. Regardless, an on-line physician, knowledgeable in diagnosing and treating AMI, should be in contact with the personnel in the field.

Regarding the choice of which thrombolytic drugs is most appropriate for prehospital use; probably any one of the drugs mentioned here would be just as efficacious as another. Each of the five drugs currently available (whether investigational or not) when given within a window of three hours or less from onset of symptoms is going to carry a relatively high rate of reperfusion. SK and TPA have the advantage of being the only two thrombolytic drugs currently available with FDA approval for treatment of AMI. On the other hand APSAC is a promising new drug that will probable receive FDA approval in the not to distant future. The advantage of APSAC when compared to the other thrombolytics is that it can be given as an IV bolus injection over about 4 minutes in contrast to prolonged IV infusions of up to 1-3 hours for the other drugs. This unique characteristic of APSAC may make it more suitable for prehospital use since its method of administration should decrease the likelihood for errors in dosing.

## CONCLUSION

Treatment of AMI has and is advancing at a rapid pace with new drugs and better methods of mechanical intervention. A time when thrombolytic therapy is almost routine in the prehospital setting will most certainly come. However, in order to do so safely and effectively, questions about the diagnostic accuracy and clinical skills of the field personnel must be resolved. Even when extreme caution is employed with administration of 2nd generation drugs by an experienced cardiologist, the risk of major drug related complications is high. This risk may prove to be too high with currently available agents, so prehospital thrombolytic therapy may have to wait for the development of third or fourth generation drugs with lesser risks of major complications. This will continue to be an exciting and controversial topic and certainly will play a key role in early treatment of AMI in the future.

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