

Healthy Heart

Volume-3 | Issue-33 | August 5, 2012

Price : ₹ 5/-

Honorary Editor :

Dr. Satya Gupta



From the desk of Editor:

As we all know, incidence of the acute myocardial infarction in India is increasing. Though we know that primary angioplasty is the gold standard treatment of Acute ST Elevation Myocardial Infarction (STEMI), most of the Indian population lives in rural areas and it is not always possible to shift the patient for primary angioplasty to a cathlab equipped hospital. This article has beautifully reviewed all available thrombolytic agents in clinical use, their dosage, mode of therapy and selection of these agents in a given situation. Urokinase is widely used thrombolytic agent in periphery; especial emphasis is given about its indication and proper dosage.

- Dr. Satya Gupta

Thrombolytic agents : selection and dosage

Concept of Reperfusion Therapy

Timely reperfusion of jeopardize myocardium represents the most effective way of restoring the balance between myocardium oxygen supply and demand. Although late spontaneous reperfusion occurs in some patients, thrombotic occlusion persists in most patients with STEMI while myocardium is undergoing necrosis. "Time is the muscle" and the salvage of myocardium is totally dependent on the speed of reperfusion therapy once the patient develop STEMI. Time dependence may be particular critical with fibrinolysis because of the decreasing efficacy of fibrinolytic agent as coronary thrombi mature over time and less responsive to thrombolysis.

Fibrinolytic Agents

1. Streptokinase (SK)
2. Urokinase (UK)
3. Tissue Plasminogen Activator
 - Alteplase (tPA)
 - Reteplase (rPA)
 - Tenecteplase

1. **Streptokinase (SK)** : Derived from group C, β -hemolytic streptococci. Not fibrin specific. Activates adjacent plasminogen by forming a non-covalent SK-plasminogen activator complex. Plasma half-life 30 min. Stimulates antibody production making retreatment difficult.
2. **Urokinase (UK)** :Derived from cultured human cells. Not fibrin specific. Activates plasminogen directly by enzymatic action. Plasma half-life 20 min.
3. **Tissue Plasminogen Activator** : Derived by recombinant genetics from human DNA. Fibrin specific. Activates plasminogen associated with fibrin directly by enzymatic action. Short plasma half-life. Three preparations of tPA are available.
 - **Alteplase (tPA)** is the glycosylated protein of 527 amino acids produced by recombinant DNA technology.
 - **Reteplase (rPA)** is the 39,571 molecular weight non-glycosylated deletion mutein of tPA. It contains

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355 of the 527 amino acids of native tPA and includes the kringle 2 and the protease domains of the parent molecule.

- **Tenecteplase** is the 527 amino acid protein produced by recombinant DNA technology. It differs from alteplase by 6 amino acids

Indications

- Acute ST-Elevation Myocardial Infarction (STEMI) : streptokinase, tPA (Alteplase, Reteplase & Tenecteplase)
- Acute ischemic stroke : tPA (Alteplase)
- Acute pulmonary embolism : SK, UK, tPA (Alteplase)
- Acute deep venous thrombosis : SK
- Clotted AV fistula and shunts : UK

Streptokinase(SK): SK remains the most common fibrinolytic agent used globally. It is usually used as a short-term infusion (30 to 60 minutes) in doses of 1.5×10^6 U and has a plasma half-life in man of ≈ 20 minutes. Within a few days, the anti-SK titer rapidly rises to 50 to 100 times the preinfusion level, remaining there for many months or even years. This makes repeated administration impractical except very early after initial dosing.

Urokinase(UK): UK is a naturally occurring 2-polypeptide chain

plasminogen activator derived from human urine and human kidney cells in culture. It produces extensive systemic fibrinolysis, is nonimmunogenic, and has achieved coronary patency rates approximating that of SK. In acute myocardial infarction, the dose of urokinase is either 2×10^6 U as a bolus or 3×10^6 U over 90 minutes, and it is cleared from plasma with an initial half-life of 6 to 9 minutes. Its principal use in North America has been for direct intracoronary infusion.

Urokinase was withheld from the market for some years because of manufacturer issues with the Food & Drug Administration (FDA), but has since been reintroduced. The package insert was revised and now carries indications only for massive PE and PE accompanied by unstable hemodynamics. During the period when urokinase was not available, the FDA encouraged the off-label use of reteplase and alteplase for local-regional lysis of venous and arterial thrombus at any location. Currently, urokinase is readily used for this purpose in different clinical and interventional settings. USFDA does not encourage use of Urokinase in Acute MI situation.

Despite being one of the first fibrinolytics tested in humans, it has little clinical trail data to support its use.

Angiographic trials conducted in the 1980s demonstrated arterial patency similar to that achieved with alteplase and generally better than that achieved with streptokinase. In terms of clinical end points, urokinase combined with heparin demonstrated no mortality benefit over heparin alone in patients with acute MI. Intra coronary urokinase administration at a rate of 6000 IU/min up to a maximum of 750,000 IU resulted in recanalization in more than 60% of patients suffering from MI. In the TIMI-5 study, IV administration of urokinase, tPA, or a combination of both achieved 62%, 71%, and 76% coronary patency rate respectively. The difference was not statistically significant. In aggregate, these data do not support the use of urokinase for treating acute MI.

Alteplase (tPA): This prototype fibrin-specific plasminogen activator has high affinity for plasminogen in the presence of fibrin and is a serine proteinase containing a single polypeptide chain of 527 amino acids. Manufactured by recombinant DNA technology, it is converted from a single- to a double-chain form by plasmin.

The recommended dose of rt-PA (alteplase) for the treatment of acute MI is 100 mg administered "front

loaded,” starting with a bolus of 15 mg followed by 50 mg in the next 30 minutes and the remaining 35 mg in the following hour. The initial half-life of rt-PA in plasma is 4 to 8 minutes. In GUSTO trial, a 15-mg IV bolus of rt-PA was administered, followed by a weight-adjusted regimen of 0.75 mg/kg over 30 minutes (not to exceed 50 mg) and then 0.50 mg/kg over 60 minutes (not to exceed 35 mg). This study conclusively demonstrated that rt-PA, a fibrin-selective molecule, was superior to SK, a non-fibrin selective agent, for both early and 1-year mortality reduction. The angiographic substudy of GUSTO also demonstrated an important relationship between the establishment of early coronary patency and survival.

Ratelase(rPA):-rPA is a single-chain nonglycosylated deletion variant consisting only of the kringle 2 and the proteinase domain of human tPA; it contains amino acids 1 through 3 and 176 through 527 or rt-PA (deletion of Val4-Glu175). The Arg275-Ile276 plasmin cleavage site is maintained. Because of the absence of the finger and kringle 2 domains, the fibrin specificity of r-PA is lower. In patients with acute MI, an initial half-life of 14 to 18 minutes was observed for r-PA.

The dose response of r-PA in patients with acute MI was evaluated in 2 open, nonrandomized pilot trials. The RAPID I trial showed that r-PA, when given as a double bolus of 10+10×10⁶ U 30 minutes apart, achieves more rapid, complete, and sustained thrombolysis

than standard-dose alteplase (100 mg over 3 hours). In the RAPID II trial, the same r-PA dose regimen yielded 90-minute reperfusion rates that were higher than those of front-loaded rt-PA (59.9% versus 45.2%, P=0.01). r-PA did not achieve superior mortality or clinical outcomes compared with SK (1.5×10⁶ U over 60 minutes) in the INJECT study. In the GUSTO III trial, which hypothesized the superiority of r-PA over rt-PA, no difference was demonstrated between these agents in 30-day mortality, hemorrhagic stroke, bleeding complications, and the combined end point of death and stroke. A 1-year follow-up in GUSTO III has recently confirmed similar mortality outcomes in the 2 treatment arms of this trial. These data underscore the multiplicity of factors

Intravenous dosing of thrombolytic agents in acute MI and their comparisons

Drug	Loading dose	Maintenance dose	Duration of infusion	Concurrent heparin	90 min patency rate (%)	TIMI grade 3 flow (%)
Streptokinase	No	1.5 million IU (45 ml Nacl)	1 hr	No	≈ 50	32
Urokinase	No	2 million(20 lacs U) bolus or 3 million(30 lacs U) over 90 min	90 min	No	≈ 50	32
t-PA Alteplase	15 mg	50 mg over 30 min* and 35 mg** 1 over next hr. (100ml sterile water)	90 min	Yes	75	54
rPA Reteplase	Given by 10 + 10 U double bolus, 10 U bolus over 2 min, wait 30 min and repeat 10 U over 2 min		34 min	Yes	75	54
Tnk-tPA Tenecteplase	30-50 mg by single bolus according to body weight		5-10 sec	Yes	75	54

*0.75 mg/Kg, not to exceed 50 mg over 30 min. **0.50 mg/Kg, not to exceed 35 mg over the Administer ASAP (within 30 minutes) after onset of acute MI

***30-50 mg IV bolus over 5 sec x1 (based on weight)

- <60 kg: 30 mg
- 60-70 kg: 35 mg
- 70-80 kg: 40 mg
- 80-90 kg: 45 mg
- >90 kg: 50 mg

beyond epicardial coronary patency that ultimately translate into patient outcomes.

Tenecteplase (TNK-tPA): Another significant tPA variant is the triple-substitution mutant tenecteplase (TNK-tPA) in which replacement of Asn117 with Gln (N117Q) deletes the glycosylation site in kringle 1, whereas substitution of Thr103 by Asn (T103N) introduces a glycosylation site but at a different locus; these modifications substantially decrease the plasma clearance rate. In addition, the amino acids Lys296-His297-Arg298-Arg299 were each replaced with Ala, which confers higher fibrin selectivity and resistance to inhibition by plasminogen activator inhibitor-1 (PAI-1). Thirty to 50 mg of weight-adjusted TNK-tPA was compared with accelerated rt-PA and revealed virtually identical 30-day (6.18% for TNK-tPA; 6.15% for rt-PA) and 1-year mortalities.

Peripheral Intra-arterial Infusion

SK: 20,000 IU bolus followed by 2,000 IU/min for 60 min.

UK: 6,000 IU/min for 1-2 hrs. (Both SK and UK should be given with concurrent systemic heparin.)

Clotted IV Catheter Clearance with UK

Inject UK 5,000 IU in 1 mL into catheter. For central venous catheter inject

Thrombolytic Therapy In Pulmonary Embolism and Deep Venous Thrombosis

Dosing Thrombolytic Agents In PE/DVT					
Drug	Indication	Loading Dose	Maintenance Dose	Duration Of Infusion	Concurrent Heparin
Streptokinase	PE	250,000 IU over 30 min,	100,000 IU/hr	24 hrs.	NO
	DVT or arterial thromboembolism	250,000 IU over 30 min	100,000 IU/hr	24-72 hrs	NO
tPA (Alteplase)	PE	None	100 mg	2hrs.	Optional
Urokinase	PE	4,400 IU/kg over 10 min	4,400 IU/kg/hr	12 hrs.	NO

5,000 IU/mL in volume equal to volume of the catheter. Allow 30-60 min for thrombolysis.

Clotted AV Cannula Clearance with SK

Inject SK 250,000 in 2 mL in each end of cannula. Clamp ends and allow 30-60 min for thrombolysis.

Thrombolytic Therapy In Ischemic Stroke

Dosing of tPA (Alteplase) In Acute Ischemic Stroke

Inclusion Criteria

- Duration of symptoms and findings less than 3 hours

- CT scan of head shows no intracranial bleeding

- Blood pressure not higher than 185/100 mm Hg (BP must be kept below 185/110 mm Hg during and after therapy)

tPA (Alteplase) Dose

- 0.9 mg/kg IV over one hour (no concurrent heparin or aspirin)

Note: Patients must be carefully selected and treated within 3 hours. Other thrombolytic agents cannot be substituted for tPA. Please refer to the reference given below before using tPA in ischemic stroke.

Interfacing Heparin And Thrombolytic Agents				
Drug	First Step	Second Step	Third Step	Last Step
SK, UK	Stop heparin Infusion	Infuse thrombolytic agent in prescribed fashion	Stop thrombolytic agent infusion	Restart heparin Infusion with or without a loading dose when APTT or thrombin time returns to less than twice normal (usually after 3-4 hours)
tPA	If it is elected to discontinue heparin during tPA Infusion for PE, follow directions for the other thrombolytic agents given above.			

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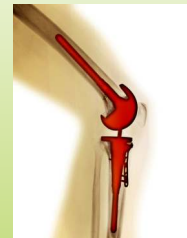


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January 4-6, 2013

Scientific Program of CIMS-CON 2013

Main Session : January 4-5, 2013 (Friday & Saturday) Venue : Tagore Hall, Ahmedabad

- | | | |
|---|---|--|
| ◆ Acute coronary syndrome (non STEMI) | ◆ CT, MR, PET and nuclear cardiovascular imaging | ◆ New devices / pre-clinical / first in - humans studies |
| ◆ Acute myocardial infarction | ◆ Device innovation and interventions | ◆ Pharmacotherapy - anticoagulants, antiplatelet, fibrinolytics |
| ◆ Angiography and QCA | ◆ Diabetes and management | ◆ Peripheral vascular disease |
| ◆ Angioplasty overview and outcomes | ◆ Debates | ◆ Renal insufficiency (acute and chronic) |
| ◆ Arrhythmias | ◆ Drug eluting balloons and local drug delivery (non stent based) | ◆ Stents - bare metal, drug eluting |
| ◆ Coronary artery disease | ◆ Electrophysiology diagnosis and therapies (including pacemakers and defibrillators) | ◆ Stroke and stroke prevention therapy |
| ◆ Cardiac surgery | ◆ Heart failure and management | ◆ Thrombus and thrombectomy (excludes atherectomy) |
| ◆ Cardiogenic shock and hemodynamic support devices | ◆ Hybrid surgical and PCI revascularization | ◆ Valvular disease |
| ◆ Cardiology guidelines | ◆ Hypertension and management | ◆ Vascular closer devices and complications - femoral / vascular access and intervention - transradial |
| ◆ General cardiology | ◆ Imaging intravascular - IVUS, OCT, spectroscopy, non IVS, non OCT | ◆ Women's health |
| ◆ Heart diseases | ◆ Inflammation and infection | ... and many more |
| ◆ Coronary complications | ◆ Ischemic heart disease | |
| ◆ Congenital heart disease - ASD, coarctation, PDA, coronary anomalies, AVF, PFO, VSD | ◆ Lipid disorders and management | |
| ◆ Coronary lesions - bifurcations, CTO, in stent restenosis, left main, small vessels | | |

**Satellite Session :
January 4, 2013 (Friday) 8.00 pm - 10.00 pm**

- ◆ Cardiac Pharmacology
- ◆ Imaging/ Diagnostics/Therapeutics
- ◆ Peripheral Vascular Disease
- ◆ Cardiology Guidelines
- ◆ Year in Cardiology / Cardiac Surgery - What Physicians Should Know ?

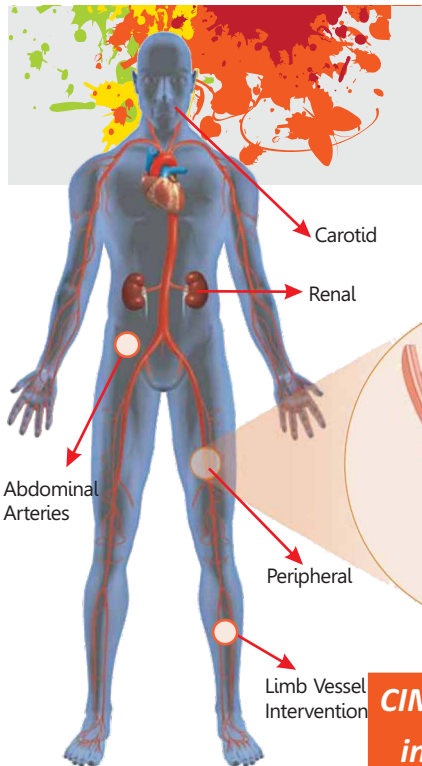
**Certification Course :
January 6, 2013 (Sunday) 9.00 am - 5.00 pm**

- ◆ Clinical Cardiology
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Endovascular Peripheral Workshop with Dr. Ashit Jain August 31 - September 1, 2012



Dr. Ashit Jain is a well known Interventional Cardiologist practicing for the past 20 years in California, USA. Graduated from University of Delhi, completed Fellowship in Interventional Cardiology and Peripheral Vascular Disease at Ochsner Medical Center in New Orleans, USA, he has developed an extensive clinical research program at Washington Hospital in Fremont, California and is involved in multiple new device research technologies. He has also served as site principal investigator on over 26 multi-center clinical research trials and has written and presented many abstracts and publications in the field. A pioneer in Carotid Interventional Programs in the San Francisco Bay area, he is affiliated with five hospitals in the East Bay of San Francisco and has personally performed over 500 carotid interventions.

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- Brachiocephalic arterial disease
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Printed, Published and Edited by Dr. Keyur Parikh on behalf of the CIMS Hospital
Printed at Hari Om Printery, 15/1, Nagori Estate, Opp. E.S.I. Dispensary, Dudheshwar Road, Ahmedabad-380004.
Published from CIMS Hospital, Nr. Shukan Mall, Off Science City Road, Sola, Ahmedabad-380060.