ISSN: 0975-766X
CODEN: IJPTFI
Available Online through ***Research Article***
www.ijptonline.com

ROLE OF RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR IN THROMBOLYSIS

Aidhal Varghese, Jesna Jacob, Teena Thariyan, L. Panayappan*, K. Krishnakumar
Pharm.D students, Department of Pharmacy Practice, St. James' college of Pharmaceutical sciences and St. James' Hospital Trust Pharmaceutical Research Centre (DSIR Recognized), Chalakudy, Kerala.
Email: panayappan76@gmail.com

Received on: 17-05-2019 *Accepted on: 22-06-2020*

Abstract

Stroke or cerebrovascular accident is the sudden interruption of blood supply to brain, which is a medical emergency condition, and prompt treatment is crucial or may lead to fatal conditions or lifelong disability. Intravenous Tissue Plasminogen Activator (t-PA) was recognised and approved as the thrombolytic agent for acute ischemic stroke that can improve patient outcome and resolve neurological deficit. Apart from stroke, t-PA showed effectiveness in treating Myocardial infarction, venous thromboembolism etc. This article review regarding role of t-PA in thrombolysis provide an in-depth understanding of the role of Tissue Plasminogen Activator as thrombolytic agent in stroke and other conditions like Myocardial infarction, Thromboembolism.

Keywords: Thrombolytic Agents, Stroke, Tissue Plasminogen Activator, Myocardial infarction, Venous Thromboembolism

Introduction: The rise of cardiovascular diseases such as stroke, Myocardial infarction, venous thrombo embolism are probably the major cause of death and disability worldwide. This medical stigma can be rectified by use of Tissue-Plasminogen Activators which specifically lyse fibrin in the vasculature. Tissue Plasminogen Activators are manufactured by using recombinant biotechnology techniques, specific recombinant t-PA (rt-PA) include Alteplase, Reteplase, Tenecteplase and the newer one Desmoteplase.

History

The production of thrombolytic agents started in 1930s and continued until 1979, when t-PA was purified by Collen and colleagues from the human melanoma cell culture.[1] In 1983 it became possible to produce rt-PA

by expression of a cloned gene, which opened the door for clinical trials to start, mainly for coronary thrombolysis.[2] In 1995, the National Institute of Neurological Disorders and Stroke(NINDS) study claimed that t-PA was an effective treatment for acute ischemic stroke, if started in less than 3 hours after symptoms onset.[3]

In 1996, the Food and Drug Administration(FDA) approved intravenous t-PA. Nowadays, in addition to acute ischemic stroke, thrombolytic therapy is considered a treatment option for acute myocardial infarction. Furthermore, studies have indicated the use of t-PA in acute renal artery thrombosis.[4]

Mechanism of Action

Tissue type plasminogen activator is a blood factor or protein orchestrating the breakdown of blood clots and it is exogenously administrated in a recombinant form in ischemic stroke patients to aid the endogenous fibrinolytic processes in dissolving the clot.[5]

Tissue plasminogen activator is a serine protease which is synthesised from endothelial cells.t-PA plays a major role in fibrinolytic system which converts plasminogen into plasmin and dissolves blood clot in the vasculature. In kinetic analysis it is revealed that in the absence of fibrin, t-PA is a poor plasminogen activator. T-PA shows two orders of magnitude higher activity in the presence of fibrin.

The timing of the treatment is very important because t-PA giving in a stroke causes bleeding inside the brain. The inhibitory action of tissue plasminogen activator is mainly by plasminogen activator inhibitor-1.

Tissue plasminogen activator can be used in both embolic and thrombotic stroke but it is contraindicated in hemorrhagic stroke as it is a blood thinner. t-PA can be manufactured using recombinant biotechnology techniques which is referred as rt-PA (recombinant tissue plasminogen activator) having longer half-life and greater binding affinity for fibrin than t-PA. Rt-PA examples include Alteplase, Reteplase, Tenecteplase.

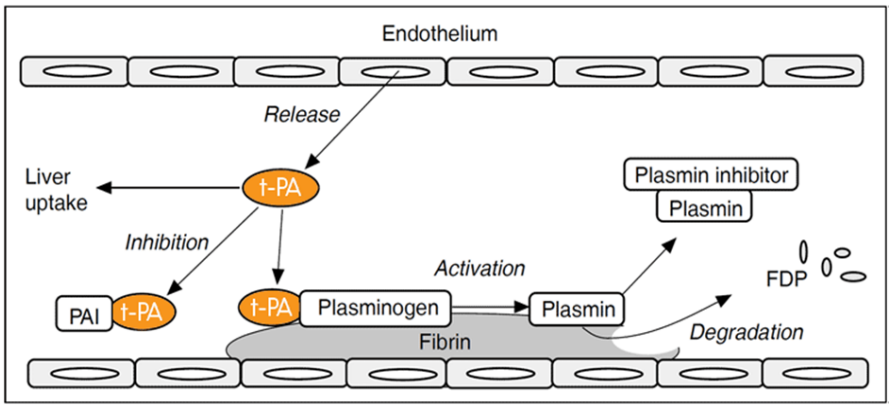

Fig1: Mechanism of action of tissue plasminogen activators.

Tissue Plasminogen Activators as Therapeutic Targets for Thrombolysis

Studies have demonstrated considerable benefit from fibrinolytics given soon after the onset of pain but little differences between streptokinase and the more expensive tissue plasminogen activator (alteplase) in reducing mortality. Fast injection of fibrin specific agents is better than slower infusion of streptokinase, especially in younger patients with anterior infarcts. Tenecteplase and Reteplase have the advantage that they can be administered by bolus injection, which facilitates pre hospital administration and reduces errors.

Alteplase: Alteplase is a tissue plasminogen activator produced by recombinant DNA technology. It belongs to class of thrombolytics or fibrinolytics and is the first drug to be indicated for treatment of Acute Ischemic Stroke for improving neurological recovery and reducing incidence of disability. Treatment should only be initiated within 3 hours after onset of stroke symptoms, not all patient with stroke will be eligible for therapy as these agents increases the risk of bleeding and is contraindicated in following conditions.

Contraindications: Evidence of intracranial haemorrhage, Suspicion of subarachnoid haemorrhage, History of intracranial haemorrhage, Uncontrolled hypertension at time of treatment (>185mm Hg systolic or >110 mm Hg diastolic), Active internal bleeding, Seizure at onset of stroke, History of bleeding diathesis, Recent major surgery within 14 days, Severe head trauma within 3 months

Dose: Adults- 0.9mg/kg of body weight, maximum dose 90mg of total dose 10% is given IV bolus, then other 90% are given as a continuous IV infusion over 60 minutes. It has to be administered as a reconstituted solution for bolus injection and then infusion. It has a very short half-life of 5 minutes.

Dosage: It is available as a lyophilised powder in 50mg and 100mg vials. Each vial is packed with diluent (sterile water for injection) for reconstitution. It is compatible with 0.9 % Nacl and dextrose 5% water.

Uses: Acute myocardial infarction – in adults for improvement of ventricular function following myocardial infarction and reduce incidence of congestive cardiac failure and mortality rate.

Pulmonary embolism for treatment of massive pulmonary embolism.

Adverse effects: The effect of drug vary with people and about 8-77% who receive alteplase for myocardial infarction was reported with bleeding, about 5% of blood loss in GI tract and 4% in genitourinary tract has also reported and 1% people show epistaxis, allergic reactions like anaphylactoid reaction, rash , urticaria are rarely reported.[6]

Tenecteplase: Tenecteplase is a thrombolytic drug which is a recombinant fibrin-specific plasminogen activator mainly indicated for reduction of mortality associated with acute myocardial infarction. Treatment should be initiated after onset of acute myocardial infarction symptoms.

Contraindications: Active internal bleeding, History of stroke, Intracranial /intraspinal surgery, Severe uncontrolled hypertension.

Dose: The recommended dose is based on patient weight, ranged from 30mg in patient weighing <60kg to 50mg in patient weighing ≥90kg, total dose should not exceed 50mg.It has a longer half life of 20-24 minutes.

Dosage: It is supplied as preservative free sterile lyophilized powder in 50mg vials under partial vaccum, accopamined by 10ml vial of sterile water for injection.

Adverse events: Bleeding, Numbness and weakness, Bloody or tarry stool, Hypersensitivity.

Reteplase: Reteplase belongs to class of thrombolytics which is a modified non-glycosated recombinant tissue plasminogen activator. It is approved for treatment of acute ST-Elevation Myocardial Infartion to reduce the risk of heart failure and death.

Contraindications: Active bleeding, recent stroke, severe uncontrolled hypertension, recent surgery.

Dose: The recommended dose for STEMI is 10 units IV over 2 minutes and administer seond dose of 10 units 30 minutes after the first dose. It has a half-life of 13-16 minutes.

Dosage: 10 units as lyophilised powder in single use vials for reconstitution co-packaged with sterile water for injection USP in 10 ml prefilled syringe.

Adverse effects: Bleeding, Hypersensitivity, Cholesterol embolization.

Comparison of Efficacy and Safety of Tissue Plasminogen Activators

Emergency rt-PA thrombolysis treatment has become one of the most effective therapeutic options available since it was first reported in 1995. It can significantly improve the clinical outcomes of patients with Acute Ischemic Stroke if applied within 3 hours.[(7)] Intravenous thrombolytic treatment with alteplase, initiated within 3 hours after the onset of symptoms, is the only medical therapy currently available for acute ischemic stroke.[(8)] While treatment with Reteplase and Tenecteplase the modified forms of alteplase are also promising nowadays.

Reteplase is a single chain deletion mutant of alteplase that seems to work more rapidly and have a lower bleeding risk. Reteplase have reduced fibrin specificity. Since reteplase have an increased plasma half-life than alteplase it is administered as double bolus followed by an infusion. In the RAPID I (Recombinant Plasminogen Activator Angiographic Phase II International Dose-finding Study) trial reteplase was superior to alteplase with respect to patency of the infarct related coronary artery.(9)

Tenecteplase is a modified variant of alteplase. It has a higher fibrin affinity and longer half-life and reduced binding to PA-1(Plasminogen activator inhibitor)-1. Tenecteplase is a promising agent for acute ischemic stroke and its pharmacokinetic profile allow single bolus administration, that is Tenecteplase requires only one-time bolus for administration, compared with 60 minutes continuous infusion required for alteplase.It have fewer major bleeding complications than alteplase. The most recent acute ischemic stroke guideline of the American Heart/Stroke Association advanced a new recommendation that Tenecteplase could be considered as an alternative to alteplase in patient with acute ischemic stroke with minor neurological impairement and no major intracranial occlusion.(10)

Conclusion

Intravenous t-PA was recognised as the approved thrombolytic agent for acute ischemic stroke that can improve patient's outcome and resolve their neurological deficit. The main reason for the difficulty of stroke treatment is the narrow time window, which leads to the small proportion of eligible patient to be treated with t-PA.

References

1. Rijken DC, Collen D.Purification and characterization of the plasminogen ctivator secreted by human melanoma cells in culture.J Biol Chem.1981;256(13):7035-41(pubmed).
2. Van de Werf F, Ludbrook PA, et al. Coronary thrombolysis with tissue type plasminogen activator in patient with evolving myocardial infarction:N Engl J Med.1984;310(10):609-13.
3. Mullen MT, Pisapia JM, et al..Systematic review of outcome after ischemic stroke due to anterior circulation occlusion treated with intravenous, intra-arterial, or combined intravenous+ intra-arterial thrombolysis, Stroke.2012:43(9):2350-5.
4. Syed MI, Shaikh A, et al. Acute renal thrombosis treated with t-PA power-pulse spray rheolytic thrombectomy. Cardiovasc Revasc Med.2010;11(4):264.el-7.

5. Iordanis Gravanis and Stella E Tsirka et al.t-PA as a therapeutic target in stroke. January 22 2008; 159-170.
6. Yadhi S, Willey JZ et al. Treatment and outcome of hemorrhagic transformation after

Intravenous alteplase in acute ischemic stroke: a scientific statement for health care

Profeesionals from the American Heart Association/ American Stroke Association. Stroke.2017:48: e343-e361.
7. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue Plasminogen Activator for Acute Ischemic Stroke: N Engl J Med 1995; 333:1581-1588.
8. Werner Hacke, M.D.,Markku Kaste, M.D., et al. Thrombolysis with Alteplase 3 to 4.5 hours after Acute Ischemic Stroke: N Engl J Med 2008; 359:1317-1329.
9. Bode C, Smalling RW, Berg G, et al. Randomised comparison of coronary thrombolysis achieved with double bolus reteplase and front loaded, accelerated alteplase in patients with acute myocardial infarction: Journal of the American Heart Association 1996; 94: 891-898.
10. Powers WJ, Rabinstein AA, et al; American Heart Association Stroke Council.2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American stroke Association. Stroke.2018;49: e46-e110.

Corresponding Author:

L. Panayappan*,

Pharm.D students, Department of Pharmacy Practice, St. James' college of Pharmaceutical sciences and St. James' Hospital Trust Pharmaceutical Research Centre (DSIR Recognized), Chalakudy, Kerala.

Email: panayappan76@gmail.com