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Tissue Plasminogen Activator in Stroke: A Review on Medical Management of Stroke and Mechanism of Action of TPA, Contraindications, Time Sensitivity

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Abstract

Stroke is a major global cause of death and disability that poses a significant public health risk. An overview of stroke is given in this abstract, with a particular emphasis on medical therapy. Stroke causes irreparable damage and localized neurological abnormalities; it is frequently the outcome of ischemia or hemorrhagic episodes. Stroke medical therapy requires a multimodal strategy. Thrombolytic therapy is the cornerstone of treatment for acute ischemic stroke, with tissue-type plasminogen activator (tPA) serving as the principal pharmacological intervention. Its effectiveness depends critically on prompt dosing during a crucial window of 4.5 hours after the onset of symptoms. Accurate diagnosis, ruling out cerebral hemorrhage, and directing treatment choices all depend on neuroimaging. Supportive care is important; it includes interventions like blood pressure monitoring, oxygenation to prevent hypoxia, and antipyretic medication to treat increased body temperature linked to a worse prognosis. Alternative therapies are being investigated, including as antiplatelet drugs and studies on the possible advantages of acute therapeutic anticoagulation.

Keywords: stroke; tissue plasminogen activator; alteplase; tenecteplase; intracerebral hemorrhage

Introduction

Stroke ranks as the fourth most common cause of death and the primary cause of disability among the elderly in the United States [1,5]. Thrombotic and embolic stroke are the two main subtypes of ischemic stroke [8,9]. Thrombotic strokes can happen in the brain's small or major blood arteries. Large cerebral arteries typically experience thrombotic strokes when a thrombus develops on top of an impaired atherosclerotic plaque [12]. When tiny blood arteries in the brain get blocked, usually due to high blood pressure, small vessel or lacunar infarcts transpire [10]. The thrombus in an embolic stroke begins outside the brain, passes through the bloodstream, and lodges in a cerebral artery. The most frequent cause of these thrombi is the heart, especially in those who have atrial fibrillation. The most common cause of acute ischemic stroke (AIS) is occlusion of a blood artery, which results in localized neurologic impairments and irreparable brain damage [1,5,6].

When evaluating a suspected ischemic stroke, the primary objective is to rule out cerebral bleeding using neuroimaging and rapid restoration of regional cerebral blood flow [1,2,6]. Secondly, one should evaluate the suitability of administering thrombolytic drugs and endovascular device therapies for acute treatment, as well as providing general supportive care has to be carried out [1].

Based on the finding that atherothrombotic and thromboembolic occlusions account for 80-90% of focal cerebral ischemic events that occur within 8-24 hours after symptom onset, thrombolytic medications are used in patients with acute ischemic stroke [2,11]. The goal of thrombolytic drugs is to restore blood flow to the ischemic area [2,3,5]. Intravenous tissue-type plasminogen activator (t-PA) is the sole approved pharmacological recommended treatment for restoring blood flow, which needs to be given within 4.5 hours of the onset of symptoms [6-8,11,15,23,24]. Tissue plasminogen activators (tPAs) are classified as serine proteases, a group of enzymes that play a critical role in breaking down proteins by cleaving peptide bonds [28]. Early in the 1990s, t-PA was used in the first clinical trial for stroke thrombolysis with the goal of determining dose verification, mechanism of action, and safety profile. Subsequently, huge double-blind, randomized, placebo-controlled trials were conducted to evaluate the effectiveness and safety of t-PA in acute ischemic stroke [15].

Thrombolytic medications are synthesized from enzymes that are found in nature, that disintegrate thrombus as a part of the cascade of spontaneous clotting. A few are taken from biological samples (such as desmoteplase and urokinase), and others (such as recombinant tissue plasminogen activator (rt-PA), also known as pro-urokinase recombinant are manufactured [5]. Advancements in recombinant biotechnology enable the production of synthetic forms of tissue plasminogen activators (tPA) known as recombinant tissue plasminogen activators (rtPA). With time, effort has been directed towards enhancing their pharmacokinetic and pharmacodynamic properties. Focus has been made towards prolonging their short half-life and increasing fibrin specificity, thereby preventing unwanted fibrinolytic states [28].

For acute ischemic stroke, intravenous thrombolysis with alteplase is the standard medical intervention [2]. In a prospective single-dose study with alteplase (rt-PA) in patients with acute thrombotic stroke, von Kummer and Hacke demonstrated the significance of established collateral anastomoses for patient outcome [2,4]. Aspirin-based antiplatelet medication, when started within 48 hours of the onset of an ischemic stroke, has been demonstrated to reduce the risk of an early recurrent stroke; however, the stroke itself is not treated by this treatment. Clinical trials for more antiplatelet medications are now being conducted, since they have demonstrated encouraging outcomes whether used alone or in conjunction with aspirin to further prevent early recurrence [1,12]. In the context of acute ischemic stroke, acute therapeutic anticoagulation using low molecular weight heparin (LMWH) and unfractionated heparin (UFH) given to unselected individuals has not shown any clinical advantages over antiplatelet medications [1,12].

Supportive Care

1. **Oxygenation:** During episodes of acute cerebral ischemia, it's critical to maintain appropriate tissue oxygenation to avoid hypoxia and possibly exacerbate the neurologic impairment [1].
2. **Antihypertensives:** Careful blood pressure control is essential before, during, and for 24 hours following the administration of alteplase (recombinant tissue plasminogen activator; rtPA) in patients who are candidates for therapy with thrombolytic drugs. After thrombolytic therapy, intracerebral hemorrhage is linked to abnormally high blood pressure [1,26].
3. **Antipyretics:** Poor neurologic prognosis has been linked to elevated body temperature in the context of acute ischemic stroke, potentially as a result of higher metabolic demands, heightened neurotransmitter release, and increased production of free radicals. Antipyretic medicine and maintaining normothermia may help individuals with severe episodes have a better prognosis [1].

Mechanism of Thrombolytic Therapy in Stroke

Activated platelets aggregate onto fibrin meshes to produce blood clots. The fibrin meshes are broken down by plasmin, a broad-spectrum protease that is found in the blood as an inactive zymogen (plasminogen) [12-14,16,17,23,27]. The temporary effects of plasmin are quickly counteracted by α2-antiplasmin, a prevalent inhibitor that restricts plasmin's function to the area surrounding the clot. The efficient conversion of plasminogen to plasmin by plasminogen activators (PAs), namely tissue-type PA and urokinase-type PA (uPA), is necessary for fibrinolysis to occur [12]. The transformation of plasminogen into active plasmin is catalyzed by the serine protease tissue-type plasminogen activator (tPA). Since the main function of plasmin in plasma is to degrade fibrin, tPA is used as a thrombolytic medication to treat ischemic stroke. Clot busting, or thrombolysis, is the process of pharmacologically dissolving blood clots. Blood flow in the blocked channel is restored upon clearance of the cross-linked fibrin mesh that forms the clot's structure. As a result, the clot becomes soluble and more vulnerable to being broken down by other proteolytic enzymes [11]. The justification for using tPA in ischemic stroke patients is that it causes the clot to dissolve, allowing the blocked blood vessel to reopen. However, the restoration of blood artery patency is only significant if the ischemic area's brain tissue remains alive. Unfortunately, brain tissue has a high metabolic activity and is therefore extremely susceptible to ischemia. It is known as the penumbra because the perimeter, which receives some perfusion from nearby non-ischemic regions, is still salvageable within a tolerable time period of a few hours, but the core of the area supplied by the occluded arterial becomes necrotic relatively quickly. This ischemic but still viable penumbra may be saved by thrombolysis by tPA through effective recanalization, but it must be given promptly [12].

Mechanism of Action of Alteplase in Stroke

The recombinant version of tissue plasminogen activator (t-PA), which is naturally produced by endothelium and other vascular cells, is known as alteplase. It was the initial licensed recombinant tissue plasminogen activator (rt-PA) for the treatment of thromboembolic disorders, such as acute massive pulmonary embolism (AMPE) and acute myocardial infarction (AIS). Alteplase catalyzes the conversion of plasminogen into plasmin by cleaving the arginine-valine link at positions 560 and 561. An active protease called plasmin breaks down thrombus into fibrin degradation products (FDP), which causes the clot to dissolve. Fibrin monomers crosslinked by lysine side chains make up thrombus. Clots are a rich source of plasminogen because of their lysine side-chain cross linkages strong affinity-binding interactions with plasminogen. Due to its strong affinity for lysine residues and resulting in the formation of tertiary complexes involving alteplase, plasminogen, and fibrin, alteplase, like desmoteplase, tenecteplase, and reteplase, is specific to fibrin [16].

Mechanism of Action of Tenecteplase in Stroke

Randomized clinical trials have shown that it has significant practical benefits in terms of administration and superior therapeutic efficacy for patients with large-vessel blockage [19]. The genetically altered form of rt-PA, called tenecteplase (TNK), is a tissue plasminogen activator (tPA) generated through DNA recombination approach utilizing a well-established mammalian cell line [20,21]. The intravenous alteplase (TPA) protein is restructured to produce tenecteplase (TNK). Through the replacement of three amino acid sites, TNK is endowed with characteristics that make it potentially more suitable for systemic thrombolysis. TNK and TPA both work via the same mechanism, although there are a few beneficial differences. Compared to TPA, it is 14 times more selective for fibrin, has a longer half-life, a slower rate of plasma clearance, and is 80 times more resistant to plasminogen activator inhibitor type 1 (PAI-1) inhibition [6,25]. Its approximately 18-minute half-life enables quick administration of a single bolus [25].

Side Effects of Tissue Plasminogen Activator and Risk of Hemorrhagic Outcomes

Through recanalization, endogenous t-PA prevented brain injury, but the protective effect declined when the blocked vessels remained closed. On investigating t-PA-induced intracerebral hemorrhage (ICH), it was found that matrix metalloproteinases (MMP-3) have a comparatively significant role in the increased ICH-induced through t-PA [15,26,27]. In endothelial cells, t-PA increased MMP-3, but this overexpression was inhibited through the suppression of low-density lipoprotein receptor-related protein (LRP) or nuclear factor kappa-B (NF-κB) activation. Consequently, t-PA induces MMP-3 in endothelial cells, which results in ICH. This could be targeted to increase the therapeutic efficacy of t-PA for acute ischemic stroke. It is regulated by the LRP/NF-κB pathway [15].

According to Nicole et al. (2001), rt-PA induces neurotoxicity by cleaving the N-methyl-D-aspartate (NMDA) NR1 subunit, which amplifies excitatory toxicity and harmful calcium excess. Rt-PA has the ability to either directly or indirectly cause a significant amount of ROS, which in turn releases thrombin and iron from blood clots and increases the expression of 4-HNE in blood vessels within the cerebral infarct according to Yamashita et al. 2009. Furthermore, Rt-PA has been shown to contribute to the destruction of the microvascular basal lamina and to exhibit acute direct cytotoxicity in blood vessels (Maeda et al. 2009) [26].

While the most common side effect of tPA is intracerebral hemorrhage (ICH) [23,25-27], other possible side effects include anaphylaxis/angioedema, systemic bleeding, and cardiac rupture are less frequent. Patients who get IV tPA within days of an acute myocardial infarction (MI) have been linked to myocardial rupture. Given the risk of pericardial bleeding and tamponade, signs of pericarditis constitute a more worrying contraindication for systemic tPA usage. Furthermore, the factors associated with the increased risk are the severity of the stroke and the existence of brain mass impact and edema on CT before therapy [25].

Contraindications of Tissue Plasminogen Activators in the Treatment of Acute Ischemic Stroke

tPAs are to be avoided in cases where the risks of bleeding and severe complications outweigh the potential benefits of the therapy. These include patients with ongoing intracranial hemorrhage (ICH), subarachnoid bleeding, and those experiencing active internal bleeding. tPAs should also be avoided in patients who have recently (within three months) undergone intracranial or spinal surgery, suffered significant head trauma, show signs of intracranial conditions that raise the bleeding risk, exhibit bleeding tendencies (hemorrhagic diathesis), or have uncontrolled severe hypertension [28-31].

Drug Interactions and Toxicity Monitoring

Drug interactions of tPAs must be monitored closely to prevent adverse effects like bleeding and hemorrhage.

Defibrotide enhances the effects of tPAs through pharmacodynamic synergy and is therefore not recommended for use together. Prothrombin complex concentrate (human) counteract the effects of tPA drugs, through pharmacological antagonism. Apixaban, when combined with tPA medications, increases anticoagulation, thereby elevating the risk of bleeding manifestations. Nitroglycerin has the potential to reduce the concentration of tPA drugs in the bloodstream. Salicylates amplify the adverse effects of thrombolytic drugs, necessitating close monitoring [28].

The FDA approved drug aminocaproic acid is used to reverse the toxicity of tPAs. It works by inhibiting proteolytic enzymes like plasmin, the primary enzyme responsible for fibrinolysis [32].

Time Sensitivity

Guidelines suggest a door-to-needle (DTN) time of 60 minutes or less. The advantages of intravenous tissue plasminogen activator (tPA) in patients with acute ischemic stroke (AIS) are time dependent. The implementation of a national quality improvement initiative was linked to a decrease in in-hospital mortality and intracranial hemorrhage, as well as an increase in the proportion of patients discharged home, and an improvement in the timeliness of tPA administration following AIS on a national scale [33]. When patients with a mismatch between baseline diffusion- and perfusion-weighted MRI findings receive intravenous tPA within a 3- to 6-hour window, there is a correlation between early recanalization at MR angiography and a favorable clinical response [34].

The time has come for all hospitals to eliminate the disparity in how stroke patients are deemed eligible for time-critical stroke therapy. Access to stroke expertise that can determine patient eligibility for thrombolysis can be obtained through easily accessible and tested methods like telemedicine, and national campaigns aim to shorten the time it takes to get a needle. Intravenous tPA should be administered to stroke patients as soon as feasible, in the same way that it would be for cardiac arrest patients [35].

Current Recommendations/Guidelines for Stroke

Criteria for Inclusion

- An ischemic stroke with a clinical diagnosis of demonstrable neurologic impairment.
- Symptoms appearing less than 4.5 hours before starting therapy; if the exact onset of the stroke is unknown, it is regarded as the last instance in which the patient was considered normal or to be at neurologic baseline.
- Aged at least 18.

Warning Signs

- Isolated neurologic problems or symptoms that are getting better quickly.
- Blood sugar level <50 mg/dL (<2.8 mmol/L).
- Severe trauma within the last 14 days.
- Significant surgery within the last 14 days.
- Seizure at the beginning of a stroke accompanied with postictal neurologic deficits.
- Pregnancy.
- Untreated, large (≥10 mm), unruptured cerebral aneurysm.

Unless there is a clinical suspicion of a bleeding abnormality or thrombocytopenia, or unless the patient is on anticoagulants or has recently received them, thrombolytic therapy should not be postponed while results are being obtained. If not, tPA injections can be administered intravenously prior to receiving coagulation test results. When the expected advantages of treating a moderate or severe stroke outweigh the expected increased risks of uterine bleeding, tPA can be used during pregnancy. Intravenous tPA looks to be safe and may be advantageous for individuals who meet these criteria, including those taking oral anticoagulants with an INR <1.7, even though these patients were excluded from the trial that demonstrated benefit in the 3-to-4.5-hour window.

According to current practice guidelines, patients who qualify for alteplase should get fibrinolysis 3-4.5 hours after the onset of symptoms. Despite the fact that alteplase has been the industry standard for more than 25 years, recent research on the use of tenecteplase as a substitute thrombolytic has demonstrated positive results. Third-generation thrombolytic drug tenecteplase is bioengineered to preserve our native tissue plasminogen activator's complete fibrinolytic function. Furthermore, tenecteplase has a 15-fold higher specificity for clot-bound fibrin than alteplase, which may lead to a decreased risk of bleeding and systemic fibrinogen depletion. These factors may contribute to tenecteplase's potential for a good safety profile [36].

Conclusion

In conclusion, this article highlights the critical function tissue plasminogen activator (tPA) plays in the treatment of acute ischemic stroke and the urgency of its administration. When administered within the crucial window of 4.5 hours after the beginning of symptoms, tPA, which is still the standard treatment for thrombolysis, greatly improves results. However, because of the significant risks associated with side effects include hemorrhagic transformation and neurotoxicity, its use necessitates careful assessment of contraindications.

Tenecteplase and other recent advancements in recombinant tPA provide intriguing substitutes because of their improved fibrin selectivity, extended half-life, and inhibitor resistance. These developments could lessen the chance of systemic hemorrhage while yet effectively reestablishing cerebral blood flow.

In addition to investigating novel thrombolytic drugs and supportive measures that might enhance tPA therapy, future studies should concentrate on maximizing the therapeutic window and reducing side effects, especially hemorrhagic events. One of the most important public health challenges is still addressing inequalities in access to time-sensitive therapies, particularly in settings with low resources.

Insight into possible advances that might influence future clinical procedures is provided by this review, which offers a thorough assessment of existing stroke care methods using tPA.

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