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STREPTOKINASE IN THROMBOLYTIC THERAPY FROM MECHANISM TO CLINICAL PRACTICE

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ABSTRACT

Streptokinase is a well-established thrombolytic agent widely used in the treatment of thromboembolic disorders such as acute myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, and neonatal thrombosis. It is a non-fibrin-specific plasminogen activator produced by β-hemolytic streptococci that promotes fibrinolysis by converting plasminogen to plasmin, resulting in clot dissolution. Despite the availability of newer fibrin-specific agents like tissue plasminogen activator, streptokinase remains extensively used in developing countries due to its cost-effectiveness and proven clinical efficacy. Experimental studies show that its thrombolytic efficiency depends on clot composition and age, while microbiological studies highlight improved production through strain selection and genetic modification techniques. Clinical investigations demonstrate improved reperfusion and metabolic recovery when streptokinase is administered early, although it is associated with higher systemic fibrinolysis and bleeding risk. Recent advances focus on recombinant approaches and combination therapies to enhance safety and efficacy, emphasizing the continued relevance of streptokinase in thrombolytic therapy.

KEYWORDS: Streptokinase, thrombolytic therapy, fibrinolysis, plasminogen activation, clot dissolution, acute myocardial infarction; neonatal thrombosis, pulmonary embolism, recombinant streptokinase, developing countries.

INTRODUCTION

Thromboembolic disorders are a major cause of morbidity and mortality worldwide, affecting both adult and neonatal populations and requiring prompt therapeutic intervention to restore blood flow and prevent tissue damage. Streptokinase is one of the earliest and most widely used thrombolytic agents, functioning as a non-fibrin-specific plasminogen activator derived from β-hemolytic streptococci that induces systemic fibrinolysis. Its affordability and broad clinical applicability have ensured its continued use, particularly in resource-limited settings. Experimental and clinical studies reveal that factors such as clot characteristics, timing of administration, and biological environment significantly influence thrombolytic outcomes. Although streptokinase is associated with a higher risk of bleeding compared to fibrin-specific agents, its effectiveness in achieving reperfusion and its economic advantages sustain its importance. Ongoing research aimed at improving production, reducing adverse effects, and enhancing therapeutic efficiency continues to expand its role in modern thrombolytic therapy. Streptokinase is a thrombolytic (fibrinolytic) agent used for the treatment of thromboembolic disorders. It is a protein enzyme obtained from β-hemolytic Streptococcus bacteria. Streptokinase acts by activating plasminogen to plasmin, an enzyme that dissolves fibrin clots. By breaking down blood clots, it helps to restore normal blood flow in blocked blood vessels. Streptokinase has been widely used in conditions such as acute myocardial infarction, pulmonary embolism, deep vein thrombosis, and arterial thrombosis. Due to its cost-effectiveness and proven efficacy, streptokinase remains an important thrombolytic agent, especially in developing countries, despite the availability of newer fibrin-specific drugs.

STREPTOKINASE AND UROKINASE DEFINITION

Streptokinase and urokinase are first-generation thrombolytic agents used for the dissolution of intravascular blood clots. Streptokinase is a bacterial protein derived from β-hemolytic streptococci and acts by forming an activator complex with plasminogen, which subsequently converts additional plasminogen into plasmin. Due to its non-fibrin specific action, streptokinase causes systemic fibrinolysis and is associated with antigenicity and allergic reactions. In contrast, urokinase is a human-derived serine protease that directly converts plasminogen into plasmin without forming myocardial infarction, a complex and is therefore non-antigenic. Both agents are effective in conditions such as acute pulmonary embolism, and deep vein thrombosis, but their clinical use requires careful monitoring because of the increased risk of bleeding.

INHIBITORS OF STREPTOKINASE AND UROKINASE

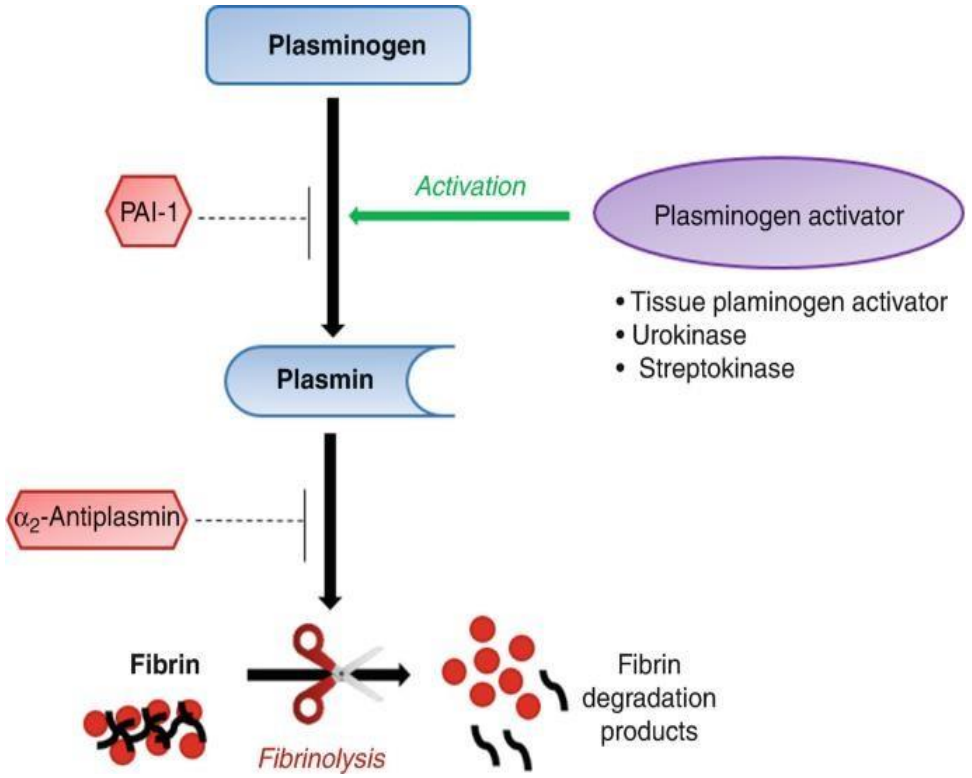
The activity of first-generation thrombolytic agents such as streptokinase and urokinase is regulated in the body by endogenous plasminogen activator inhibitors, mainly plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2 (PAI-2). These inhibitors prevent excessive fibrinolysis by blocking the conversion of plasminogen to plasmin. Urokinase is directly inhibited by PAI-1, which forms a stable inactive complex with the enzyme, thereby reducing its thrombolytic efficacy. In the case of streptokinase, since it acts by forming a complex with plasminogen, its activity is indirectly reduced by inhibitors of plasmin such as α_2- antiplasmin, which rapidly inactivates free plasmin in circulation. Additionally, streptokinase is strongly inhibited by circulating anti-streptokinase antibodies, formed due to prior streptococcal infections, leading to reduced effectiveness and risk of allergic reactions. Thus, physiological inhibitors and immune-mediated mechanisms play an important role in limiting the therapeutic action of streptokinase and urokinase.

MECHANISM OF ACTION OF THROMBOLYTIC AGENTS

Thrombolytic agents act primarily by converting plasminogen into its active form, plasmin, thereby initiating fibrinolysis. Activated plasmin degrades the fibrin meshwork of the thrombus, resulting in clot dissolution. This fibrin degradation leads to breakdown of both fibrinogen and fibrin, producing soluble fibrin degradation products. Streptokinase differs from other thrombolytics in that it does not possess intrinsic enzymatic activity. Instead, it forms a stable complex with circulating plasminogen. This streptokinase– plasminogen complex induces a conformational change that exposes the active site of

plasminogen, converting it into active plasmin. The generated plasmin then catalyzes extensive fibrinolysis, leading to lysis of intravascular thrombi and restoration of blood flow in occluded vessels.

Keywords: Plasminogen → Plasmin, Streptokinase–plasminogen complex, Fibrin degradation, Clot lysis, Fibrinolysis.

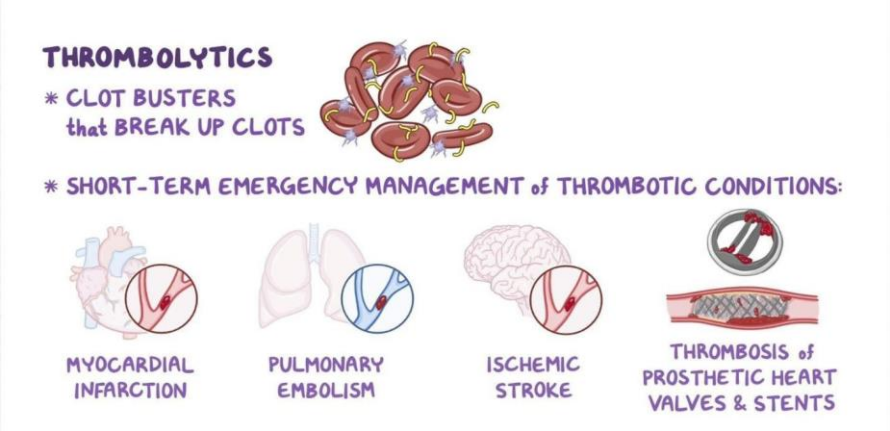


Pharmacological Effects of Thrombolytic Agents

Thrombolytic agents exhibit several important pharmacological actions that contribute to their therapeutic efficacy. They cause rapid dissolution of fibrin-rich thrombi and restore blood flow in occluded arteries and veins. By re-establishing perfusion, these agents reduce myocardial ischemia, limit infarct size, and preserve ventricular function in patients with acute myocardial infarction. Improved tissue perfusion also enhances organ function and reduces morbidity associated with thromboembolic events.

Classification of Thrombolytic Agents

- Bacterial origin: Streptokinase
- Human-derived enzymes: Urokinase
- Recombinant agents: Tissue plasminogen activator (tPA), Alteplase, Reteplase, Tenecteplase



Manufacturing of Streptokinase

Streptokinase is manufactured by fermentation using a selected strain of β- hemolytic streptococci, mainly Streptococcus equisimilis. The organism is first grown in a suitable nutrient medium to prepare the inoculum. This inoculum is then transferred to a fermenter containing a sterile culture medium with appropriate carbon and nitrogen sources. Fermentation is carried out under controlled conditions of temperature (around 37°C), pH (7.0– 7.5), and aeration. During fermentation, streptokinase is produced as an extracellular enzyme and released into the culture medium. After completion of fermentation, the broth is centrifuged or filtered to remove bacterial cells. The streptokinase present in the supernatant is purified by precipitation, dialysis, and chromatographic techniques. The purified product is then concentrated, sterilized by membrane filtration, and finally lyophilized to obtain streptokinase in a stable dry form. The finished product is filled aseptically into sterile vials and stored under refrigerated conditions.

Therapeutic Uses of Thrombolytic Agents

Streptokinase is a thrombolytic agent widely used in the treatment of acute clinical conditions caused by the formation of blood clots. It is primarily indicated in acute myocardial infarction, where early administration helps in dissolving the clot in the infarct-related

coronary artery, achieving rapid reperfusion, restoring blood flow, and reducing myocardial damage. In pulmonary embolism, streptokinase aids in breaking down large emboli, thereby improving pulmonary circulation and respiratory function. It is also useful in the treatment of deep vein thrombosis (DVT) to dissolve thrombi in deep veins and prevent post-thrombotic complications such as pulmonary embolism. In selected patients with acute ischemic stroke, thrombolytic therapy given within the defined therapeutic window can improve neurological outcomes. Additionally, streptokinase is employed in arterial thrombosis and embolism, including peripheral arterial occlusion, and is used to clear clots in occluded intravenous catheters, vascular catheters, and arteriovenous shunts. Overall, streptokinase plays a vital role in emergency thrombolytic therapy by rapidly dissolving fibrin clots and restoring normal blood circulation.

Adverse effects of Streptokinase (Thrombolytic agent)

Streptokinase therapy is associated with several adverse effects, mainly due to its potent fibrinolytic action and antigenic nature. The most common and serious adverse effect is bleeding, which may range from minor bleeding at injection sites to severe hemorrhage such as gastrointestinal bleeding, intracranial hemorrhage, or hematuria. Allergic reactions are also common because streptokinase is of bacterial origin; these reactions may include fever, chills, rash, urticaria, bronchospasm, and anaphylaxis. Hypotension may occur during or after infusion, especially with rapid administration. Patients may also experience nausea, vomiting, and headache. Due to the development of antibodies, repeated administration of streptokinase can reduce its efficacy and increase the risk of hypersensitivity reactions. Rarely, reperfusion arrhythmias may occur following thrombolysis in myocardial infarction. Therefore, careful patient selection and monitoring are essential during streptokinase therapy.

Contraindications of Thrombolytic Therapy

Despite their clinical benefits, thrombolytic agents are associated with a significant risk of bleeding. Active internal bleeding is a major contraindication to thrombolytic therapy. Patients who have undergone recent surgery or experienced severe trauma are at increased risk of hemorrhage. A prior history of hemorrhagic stroke is considered an absolute contraindication.

Uncontrolled hypertension markedly increases the risk of intracranial bleeding. Bleeding disorders such as hemophilia, recent intracranial surgery, or the presence of brain tumors further contraindicate the use of thrombolytic agents. Previous exposure to streptokinase may result in antibody formation, leading to allergic reactions and reduced efficacy upon repeated administration.

CONCLUSION

Streptokinase remains a cornerstone of thrombolytic therapy, particularly in resource- limited settings, despite the emergence of newer fibrin-specific agents. Its well-established mechanism of action—indirect activation of plasminogen leading to effective fibrinolysis—has demonstrated significant clinical benefit in the management of acute myocardial infarction, pulmonary embolism, deep vein thrombosis, ischemic stroke, and neonatal thrombosis. Extensive experimental and clinical evidence confirms that early administration, clot characteristics, and patient selection critically influence therapeutic success.Although streptokinase is associated with limitations such as systemic fibrinolysis, bleeding risk, antigenicity, and reduced efficacy upon repeated use, its affordability, wide availability, and proven efficacy continue to justify its clinical relevance. Advances in microbial strain selection, recombinant production, and combination therapeutic strategies aim to enhance its safety profile and thrombolytic efficiency.In conclusion, streptokinase continues to play an important role in modern thrombolytic practice. Ongoing research and technological improvements are expected to further optimize its clinical utility, ensuring that this first-generation thrombolytic agent remains a valuable and accessible option for the treatment of thromboembolic disorders worldwide.

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