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A Comprehensive review of alteplase and its uses.

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ABSTRACT
Alteplase, also known as tissue plasminogen activator (tPA), is a medication used to treat blood clots .It works by activating the body's natural clot-dissolving system. Alteplase helps . breakdown the clot and restore blood flow, which can be crucial in conditions like heart attack and strokes. This review gives a descriptive view of alteplase and its mechanism of action, clinical applications and safety profile.
This article also discusses the current guidelines and recommendations for alteplase administration in different clinical scenarios, including dosing regimens, contraindications, precautions. Additionally, it highlights ongoing research in the field, such as the investigation of alteplase in other thrombotic disorders and the exploration of alternative thrombolytic agents.
KEYWORDS: Alteplase, tissue plasminogen activator, fibrinolysis, ischemic stroke, haemorrhagic stroke, activase.

I. INTRODUCTION

Alteplase,also known as tissue plasminogen activator or tPA. Alteplase is a medication that's used to treat blood clots,and it's a type of thrombolytic medication.Its main job is to break down the clot and restore blood flow in conditions like acute ischemic stroke,acute myocardial infarction (heart attack),and pulmonary embolism.It does this by targeting fibrin,which is a key component of blood clots.By converting plasminogen to plasmin, alteplase helps dissolve the clot and restore blood flow. However,it's important to note that alteplase should only be used under the guidance of a healthcare proffesional,as it carries certain risks ,such as the potential for bleeding complications. Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke,but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established.We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke. Alteplase is the same as the normal human plasminogen activator produced in vascular endothelial cells and is synthesized via recombinant DNA technology in chinese hamster ovary cells (CHO).Alteplase causes the breakdown of a clot by inducing fibrinolysis.Depending on the severity of the condition ,there are different treatments available for thrombosis.Some patients may require surgery for an illness caused by thrombosis.In other instance ,there are thrombolytic or fibrinolytic drugs that can be used as medical therapy to dissolve blood clots.While there are two significant families of thrombolytic medications that can be utilized in thrombolytic therapy,alteplase,a recombinant tissueplasminogen activator ,is the preferred medication for treatment of acute ischemic stroke .

HISTORY

Alteplase is a drug derived from recombinant DNA technology .It is produced by genetically engineering cellsto produce tissue plasminogen activator (tPA),which is the active component of alteplase .This process allows for the large -scale production of alteplase in a controlled and consistent manner. The recombinant DNA technology used to create alteplase has revolutionized the production of therapeutic proteins, making them more readily available for medical use. It is the same as the normal human plasminogen activator produced in vascular endothelial cells and is synthesized via recombinant DNA technology in Chinese hamster ovary cells (CHO).

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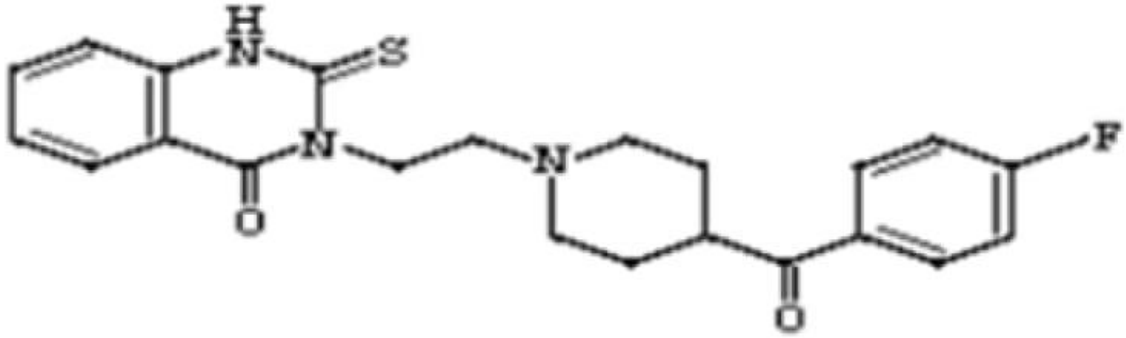
STRUCTURE OF ALTEPLASE



Brand name :activase,cathflo, cathflo activase
Generic name :alteplase t-PA, rt-PA

INDICATIONS

Alteplase is a thrombolytic agent that is manufactured by recombinant DNA technology.it is FDA approved for use in acute ischemic stroke, pulmonary embolism, acute myocardial infarction, and occluded catheters. Off – label indications include catheter directed thrombolysis in the treatment of peripheral arterial occlusive disease and deep vein thrombosis.

MEDICAL USES

Alteplase is indicated for the treatment of acute ischemic stroke, acute myocardial infarction, acute massive pulmonary embolism, and blocked catheters.similar to other thrombolytic drugs, alteplase is used to dissolve clots to restore tissue perfusion. Generally, alteplase is delivered intravenously into the body. To treat blocked catheters alteplase is administered directly into the catheter.

Ischemic stroke ; In adults diagnosed with acute ischemic stroke, thrombolytic treatment with alteplase is the standard of care. Administration of alteplase is associated with improved functional outcomes and reduced incidence of disability. Alteplase used in conjunction with mechanical thrombectomy is associated with better outcomes.

Pulmonary embolism ; Alteplase is the most commonly used medication to treat pulmonary embolism.Alteplase has a short infusion time of 2 hours and a half life of 4-6 minutes. Alteplase has been approved by the FDA, and treatment can be done via systemic thrombolysis or catheter directed thrombolysis.

Blocked catheters ; Alteplase can be used in small doses to clear blood clots that obstruct a catheter, reopening te catheter so it can continue to be used. Catheter obstruction is commonly observed with a central venous catheter. It is effective and low risk for treating blocked catheters in adults and children. Overall, adverse effects of alteplase for clearing blood clots are rare. Offer the advantage of shorter dwell times than alteplase.

ROUTE OF ADMINISTRATION

Alteplase is for intravenous administration only. Alteplase is available as a lyophilized powder in 50 mg and 100 mg vials. Each vial gets packaged with diluted (sterile water for injection) for reconstitution. It also is compatible with 0.9 % sodium chloride (NS) and dextrose 5% water (D5W). Alteplase is administered intravenously at a conncentration of 1 mg/ml for the treatment of acute ischemic stroke, pulmonary embolism, and myocardial infarction. The reconstituted solution is stable for 8 hours at room temperature. For catheter clearance, the drug is instilled directly into the catheter at a concentration of 1 mg /ml.

MECHANISM OF ACTION

Alteplase blinds to fibrin in a blood clot and activates the clot bound plasminogen.Alteplase cleaves plasminogen at the site of its Arg561-Val562 peptide bond to form plasmin. Plasmin is a fibrinolytic enzyme that cleaves the cross -links between polymerized fibrin molecules, causing the blood clot to break down and dissolve, a process called fibrinolysis.

Regulation and inhibition :

Plasminogen activator inhibition 1 stops alteplase activity by binding to it and forming an inactive complex, which is removed from the bloodstream by theliver. Fibrinolysis by plasmin is extremely short lived due to plasmin inhibitors which inactivate and regulate plasmin activity.

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PHARMACOKINETICS

Absorption:

Healthy volunteers with a baseline endogenous tissue plasminogen activator (t-PA) of 3.3 ng/ml had a 290 fold increse in baseline concentrations after receiving alteplase at an infusion rate of 0.25 mg/kg for 30 min ; with an infusion rate of 0.5 mg/kg , a 550 fold increase was observed . Acute myocardial infarction patients (n=12) given 10 mg of alteplase in a 2 minutes infusion reached a peak plasma concentration of 3310 ng/ml. This was followed by 50 mg of alteplase in 1h and 30 mg in 1.5 h, resulting in steady state plasma levels of 2210 ng/mg and 930 ng/ml,respectively.

Metabolism :

Alteplase is mainly metabolized by the liver. The carbohydrate and polypeptide domains of alteplase interact with hepatic glycoprotein receptors, leading to receptor mediated endocytosis. In vivo studies suggest that alteplase follows zero – order kinetics, meaning that its metabolism is saturable at higher plasma concntrations.

Elimination :

In healthy volunteers, more than 80% of alteplase is eliminated through urine18 hours after administration.

Volume of distribution :

The intial volume of distribution approximates plasma volume. The average volume of distribution of the central compartment goes from 3.9 to 4.3 L, and the volume of distribution at steady state goes from 7.2 to 12 L.

Half life :

Alteplase has an intial half life of less than 5 minutes in patients with acute myocardial infarction (AMI). The dominant intial plasma half life of the 3 hour and the accelerated regimens for AMI are similar.

Clearance :

Alteplase has aplsma clearance between 380 and 570 mL /min.

ADVERSE DRUG REACTION

Adverse effects of alteplase include bleeding, angoedema, anaphylaxis, and fever.

The risk of bleeding is highest in patients with the following conditions: recent intracranial hemorrhage, major surgery ,cerebrovascular diseases, recent trauma or major bleeding, unconditional hypertension, acute pericarditis,hemorrhagic opthalmic conditions, advanced age, concurrent anticoagulant or antiplatelet agents, and any coagulopathy that makes patients more susceptible to bleeding.

There have been case reports of cholestrol embolization in patients treated with thrombolytics, including alteplase. The incidence and clinical significance of this are not well defined.

DRUG INTERACTIONS

Drug-Drug interactions

- Abciximab : The risk or severity of bleeding can be increased when abciximab is combined with alteplase.
- Aceclofenac : The risk or severity of bleeding and hemorrhage can be increased when aceclofenac is combined with alteplase.
- Acemetacin : The risk or severity of bleeding and hemorrhage can be increased when alteplase is combined with acemetacin.
- Acenocoumarol : The risk or severity of bleeding can be increased when alteplase is combined with acenocoumarol.
- Acetylsalicylic acid : Acetylsalicylic acid may increase the anticoagulant activities of alteplase.

Food interactions

Avoid herbs and supplements with anticoagulant /antiplatelets activity. Examples include garlic, ginger, biberry, danshen, piracetamin,and ginkgo biloba.

CONTRA INDICATIONS

When considering alteplase for the treatment of acute ischemic stroke, do not use it in patients with the following conditions ;

- Intracranial hemorrhage
- Subarachnoid hemorrhage
- Internal bleeding
- Stroke within the least three months
- Intracranial or intraspinal surgery within the least three months
- Serious head trauma within the least three months
- Intracranial neoplasms, arteriovenous malformations, or aneurysms
- Conditions that increase the risk of bleeding
- Currently severe uncontrolled hypertension

Alteplase is FDA pregnancy category C. research has not shown whether it crosses the placenta or gets excreted in human milk. It has not had much research in pregnant women, nursing mothers, or pediatric patients.

TOXICITY

Toxicity information regarding alteplate is not readily available. Patients experiencing an overdose are at an increased risk of severe adverse

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effects such as risk of bleeding and thromboembolic events. Symptomatic and supportive measures are recommended. The carcinogenic potential of alteplase or its effect on fertility have not been evaluated. In vivo studies evaluating tumorigenicity and in vitro studies evaluating mutagenicity were negative. It has been estimated that the acute oral and dermal toxicity of alteplase is above 5,000 mg/kg.

MONITORING PARAMETERS

Patients require assessment for bleeding and hypersensitivity reactions. Neurological status and blood pressure require monitoring during intravenous threrapy. Laboratory parameters to follow include hemoglobin,hematocrite,platelets,fibrinogen,and activated partial thromboplastin time. If serious bleeding occurs, stop the alteplase therapy and provide supportive care.if a hypersensitivity reaction occurs, stop the alteplase and provide supportive therapy such as antihistamines and corticosteroids. Coagulation tests may be unreliable during alteplase therapy because alteplase may degrade fibrinogen in blood samples.

II. CONCLUSION

Alteplase, also known as tissue plasminogen activator (tPA), is a thrombolytic medication used to treat blood clots. It is commonly used in conditions such as ischemic stroke, deep vein thrombosis, and pulmonary embolism. Alteplase works by activating the body's natural enzyme callled plasmin, which helps dissolve the clot and restore blood flow. It is typically administered through an intravenous (IV) line by healthcare professionals in a hospital setting. It's important to note that alteplase should be used under the guidance and supervision of a health care professional due to potential risks and side effect.

Alteplase should only be used under the guidance and supervision of a healthcare profesional. They will determine if alteplase is the appropriate treatment for your condition.

Alteplase is typically administered through an intravenous (IV) line in a hospital setting. The dosage and duration of treatment will be determined by your healthcare provide.

It's important to inform the healthcare provider about any medical conditions or medications you are currently taking, as they may affect the use of alteplase.

Alteplase is most effective when administered as soon as possible after the onset of symptoms. Therefore, it's crucial to seek medical attention promptly if you suspect a blood clot related condition.

During treatment with alteplase, the healthcare provider will closely monitor the condition and may perform regular blood tests to assess its efffectiveness and ensure your safety.

REFERENCES

[1]. Mosimah CI, Murray PJ, Simpkins JW. Not all clots are created equal : a review of deficient thrombolysis with tissue plasminogen activator (tPA) in patients with metabolic syndrome. Int J Neurosci 2019 Jun ;129 (6): 612-618.

[2]. Seifried E, Tanswell P, Ellbruck D, Haerer W, Schmidt A: Pharmacokinetics and haemostatic status during consecutive infusions of recombinant tissue type plasminogen activator in patients with acute myocardial infarction. Thromb Haemost 1989 Jun 30;61 (3);491-501.

[3]. FDA Approved Drug products :ACTIVASE (alteplase) injection for intravenous use.

[4]. Acheampong P, Ford GA: Pharmacokinetics of alteplase in the treatment of ischemic stroke. Expert Opin Drug Metab Toxical. 2012 Feb; 8(2):271-81.

[5]. Genentech : ACTIVASE (alteplase) SDS.

[6]. "Cathflo Activase – alteplase injection ,powder, lyophilized, for solution". DailyMed.6 September 2019. Archived from the original on 29 January 2021. Retrieved 14 November 2020.

[7]. "Alteplase Monograph for Professionals" Drugs. Com. Archived from the original on 27 August 2020. Retrieved 11 November 2019.

[8]. "Activase -alteplase Kit". DailyMed. 5 December 2018. Archived from the original on 11 January 2017. Retrived 4 January 2020.

[9]. Powers WJ,Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC,Becker K,et al.(December 2019). "Guidelines for the Early Management of Patients with Acute Ischemic stroke : 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic stroke : A Guideline for Healthcare Professionals From the American Heart Association /American Stroke Association".Stroke. 50(12):e344-e418.

[10]. Jilani TN, Siddiqui AH (April 2020). "Tissue plasminogen Activator".StatPearls. Treasure Island (FL):StatPearls Publishing. Archived from the original on 29 January 2021.Retrived 10 November 2020.
[11]. O'Gara PT, Kushner FG,Ascheim DD,Casey DE,Chung MK,de Lemos JA,et al. (January 2013). "2013 ACCF/AHA guideline for the management of ST- elevation myocardial infarction : a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". Circulation. 127 (4) :e362-425.
[12]. Reed M, Kerndt CC, Nicolas D (2020).Alteplase.StatPearls. Treasure Island (FL) : Archived from the original on 29 January 2021. Retrived 30 October 2020.
[13]. Demaerschalk BM, Kleindorfer DD, Adeoye OM, Demchuk AM, Fugate JE,Grotta JC,et al. (February 2016). "Scientific Rationale for the Inclusion and Exclusion Criteria for Intravascular Alteplase in Acute Ischemic Stroke : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association". Stroke. 47 (2) : 581-641.
[14]. Powers WJ (July 2020). Solomon CG (ed.). "Acute Ischemic Stroke". The New England Journals of Medicine. 383 (3): 252-260.
[15]. Ucer EY (June 2019). "Update on ThrombolyticTherapy in Acute Pulmonary Thromboembolism".The Eurasian Journal of Medicine. 51 (2) : 186-190.
[16]. Mistry EA, Mistry AM, Nakawah MO,Chitale RV,James RF, Volpi JJ,et al . (September 2017). "Mechanical Thrombectomy Outcomes With and Without Intravascular Thrombolysis in Stroke Patients : A Meta – Analysis". Stroke. 48 (9): 2450-2456.
[17]. Martin C,Sobolewski K, Bridgeman P, Boutsikaris D (December 2016). Systemic Thrombolysis for Pulmonary Embolism : A Review . P&T.41(12): 770-775.