Tachykinins *see* Kinins and Neuropeptides: Tachykinins.

Theophylline *see* Bronchodilators: Theophylline.

**THROMBOLYTIC THERAPY**

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**Abstract**

Thrombolytic therapy, which involves the administration of agents designed to increase fibrinolytic capacity, has been utilized in respiratory medicine for more than 50 years. A variety of agents have been used to effect thrombolysis, including urokinase plasminogen activator (uPA) and streptokinase. Tissue plasminogen activator (tPA) has also been used to effect thrombolysis. Both uPA and tPA are endogenous fibrinolysins that are detectable in plasma and extravascular fluids that accumulate in the setting of inflammation. uPA is the major plasminogen activator present in bronchoalveolar lavage of normal subjects and accounts for the fibrinolytic activity that is detectable in these fluids. These agents are all characterized by a short half-life in plasma, and their effects are mitigated by inhibition attributable to the plasminogen activators, particularly plasminogen activator inhibitor-1, and by downstream antiplasmins. Thrombolytic therapy has been used to clear pathologic fibrin deposition in both extracellular and intravascular compartments. These agents are used to relieve intrapleural loculations associated with parapneumonic effusions and organizing hemothoraces. Thrombolytic therapy has also been used to treat pulmonary embolism associated with hemodynamic compromise. In both instances, the role of thrombolysis in pulmonary medicine continues to evolve based on recent and ongoing investigations.

**Introduction**

Thrombolytic therapy – therapy that increases fibrin clearance – has been used in the practice of respiratory medicine for a number of years. More than half a century ago, Tillett and Sherry inferred that intrapleural organization in the setting of parapneumonic effusions or hemothoraces was initiated by intrapleural fibrin deposition and that the process could be mitigated by the local administration of agents that would increase fibrinolysis. These investigators found that the intrapleural administration of either streptokinase or streptodornase effectively cleared pleural loculations associated with either parapneumonic effusions or hemothoraces. These observations supported the subsequent use of fibrinolytic agents to prevent intrapleural loculation and lung entrapment.

A number of uncontrolled studies subsequently supported the administration of fibrinolytic agents to address intrapleural loculations. For example, in a study done in the 1970s, Bergh and colleagues used streptokinase to treat loculations in patients with hemothoraces or parapneumonic effusions. They reported that streptokinase increased lung expansion and drainage of pleural fluid. A number of other uncontrolled studies employed streptokinase or urokinase as interventional agents and affirmed these findings using drainage or the requirement for surgical intervention as endpoints.

The relatively few randomized, controlled clinical trials that have been conducted likewise support the use of intrapleural fibrinolysins to relieve intrapleural loculations. In one such trial, intrapleural streptokinase administered in three daily doses facilitated pleural drainage and radiographic improvement of intrapleural loculations due to empyema. In this trial, 24 patients were randomized and received either intrapleural saline or streptokinase daily over 3 days. Only patients in the control group (*n* = 3) required surgical intervention, and systemic fibrinolysis or bleeding did not occur in the streptokinase-treated patients. In another controlled trial, urokinase instillation was found to be superior to saline administration in patients with multiloculated effusions.
The use of thrombolytic therapy for pleural loculation has been challenged. In one study of patients with complicated pleural effusions or empyema, drainage was increased in patients treated with streptokinase but there was no difference in requirement for surgery, time to defervescence, and duration of hospitalization. This study raises questions about the broad efficacy of intrapleural fibrinolysis, a position that was initially offered by Cameron. A review of randomized trials of patients with complicated parapneumonic effusions or empyema who had not had prior surgical intervention cast further doubt on the efficacy of intrapleural fibrinolysins. A large multicenter clinical trial meeting compared the efficacy of intrapleural streptokinase or placebo in several hundred patients with complicated parapneumonic effusion or empyema and similarly found no benefit in terms of the same endpoints.

Thrombolytic therapy has also been used for a number of years in the treatment of pulmonary emboli and in extensive ileofemoral thrombosis. Although thrombolytic therapy has been shown to decrease the incidence of the postphlebitic syndrome in patients with proximal deep venous thrombosis, its application in these circumstances has been limited because of the risk of serious bleeding or intracranial hemorrhage. Based on a similar risk–benefit analysis, the use of thrombolytic therapy in pulmonary embolism remains the subject of ongoing debate. It is generally accepted that patients who present with acute pulmonary embolism associated with shock or who develop hemodynamic compromise based on pulmonary vascular obstruction should be treated with thrombolytic therapy or, alternatively, with pulmonary embolectomy. In a meta-analysis of all available randomized trials comparing thrombolytic therapy with acute pulmonary embolism, there was a significant reduction in recurrent embolism or death in trials that included patients with hemodynamic compromise but not in trials that excluded such patients. In this analysis, most of the trials revealed an increase in major bleeding, but the increment was not statistically significant. The risk of hemorrhage with thrombolytic therapy of patients with pulmonary embolus was increased in a prior meta-analysis.

In patients with submassive pulmonary embolism and normal blood pressure, the use of thrombolytic therapy remains controversial. In a randomized, double-blind trial of thrombolytic therapy plus heparin versus heparin for patients with pulmonary embolism and pulmonary hypertension or right ventricular dysfunction without systemic hypotension or shock, the addition of thrombolytic therapy reduced the need for an escalation of therapy, including repeat thrombolysis or infusion of pressors. Some authorities interpret these observations as supporting the application of thrombolytic therapy for these patients, whereas others continue to believe that thrombolytic therapy, with its associated risk of hemorrhage, should be reserved for patients with massive pulmonary embolism and hemodynamic compromise.

A number of thrombolytic agents, including uPA, tPA, and streptokinase, have been used for intrapleural applications and to treat pulmonary embolism. When used in the recommended doses and at recommended dosage schedules, these agents appear to be of comparable efficacy. It appears that administration of any plasminogen activator can relieve pulmonary vascular obstruction in the setting of severe pulmonary embolus and that relatively short courses, delivered over a few hours, can reduce pulmonary vascular resistance. Interestingly, controlled trials have not shown any differences in the mortality of patients with pulmonary embolus who were treated with either heparin or plasminogen activators. However, the results may reflect the relatively small numbers of patients evaluated and lack of stratification for severity. Catastrophic events, including severe bleeding or intracranial hemorrhage, can occur with the use of any of the thrombolytic agents when used for the treatment of pulmonary embolus. Intrapleural administration is generally well tolerated. Intrapleural hemorrhage generally does not occur, and systemic fibrinolysis is not generally induced.

**Chemical Structure of Thrombolytic Agents**

Streptokinase is a single-chain glycoprotein with a molecular weight of approximately 50 kDa. The molecule does not exhibit intrachain disulfide bonds. This plasminogen activator is exogenous, not normally found in the circulation. It was originally isolated from β-streptococci and was first characterized in the 1940s.

Cells secrete uPA as a proenzyme known as single-chain or pro-urokinase, which has a molecular weight of approximately 54 kDa and can be activated by plasmin. The active forms of uPA include a high-molecular-weight, 54 kDa two-chain form and a low-molecular-weight form of approximately 33 kDa. Disulfide bonds connect the two chains of the high-molecular-weight form. uPA is an endogenous plasminogen activator that can be detected in circulating blood. A recombinant form has been reintroduced in clinical practice for the treatment of pulmonary embolus. uPA is mainly involved in
extravascular remodeling of transitional extravascular fibrin, as occurs in the setting of tissue injury or neoplasia, whereas intravascular fibrinolytic capacity is largely maintained by tPA.

tPA is also a serine protease plasminogen activator. It is a glycosylated enzyme of molecular weight 68 kDa (Figure 1). Like uPA, tPA can be detected in plasma and in extravascular exudates following lung or pleural injuries. The recombinant form of the molecule that is used in clinical practice differs from the endogenous molecule and exhibits differences in the distribution of its component kringle domains.

Mode of Action

Unlike uPA or tPA, streptokinase is not an enzyme, nor does it directly convert plasminogen to plasmin. Rather, streptokinase initially forms a complex with plasminogen, which is then capable of cleaving it at the Arg560–Val561 bond to generate plasmin from both complexed and free plasminogen (Figure 2). Interestingly, both uPA and tPA cleave plasminogen at this same bond to generate plasmin. The activity of the streptokinase–plasminogen complexes appears to be influenced by a number of factors, including proteolytic cleavage of the streptokinase and differential activity of the fragments combined with...
different forms of plasminogen and the interaction of the complexes with fibrin degradation products and inhibitors. Streptokinase is immunogenic and generates antibody formation and is likewise associated with febrile reactions. The plasminogen activators all have short half-lives and are cleared from the plasma within minutes. Whether given by the intravenous or the intrapleural route, uPA or tPA are subject to inhibition by the plasminogen activators, mainly plasminogen activator inhibitor-1. The fibrinolytic effects of these plasminogen activators, as well as that of streptokinase, are likewise subject to inhibition by antiplasmins (Figure 3). These features necessitate intravenous administration over intervals that vary according to the agent used. Differing dosage thrombolytic schedules have been used in the treatment of pulmonary embolism, as reviewed elsewhere. Many clinicians have become accustomed to using recombinant tPA in the setting of severe pulmonary embolism associated with hemodynamic compromise, based on familiarity with this agent. Recombinant tPA is generally administered at a dose of 100 mg, including a 10 mg initial bolus followed by administration of the balance of the dose by continuous infusion over 2 h. Most of the research concerning the use of local thrombolytic therapy for intrapleural loculations has involved the use of repeated intrapleural doses of either streptokinase or uPA. Typical daily doses for intrapleural applications have been 250 000 IU of streptokinase or 100 000 U of uPA.

Contraindications

All systemically administered thrombolytic agents carry the risk of severe bleeding, of which intracranial hemorrhage is the most feared complication. The risk of intracranial hemorrhage is approximately 1.9% in patients treated for pulmonary embolism, and the risk of major bleeding has been reported to be as high as 22%. These observations strongly speak to the need to carefully select patients most likely to benefit versus those most at risk for complications from systemic thrombolytic therapy. A number of contraindications have been identified and are listed as exclusion criteria by the American Heart Association. These exclusions include active internal bleeding, excluding menses within 21 days, or history of cerebrovascular, intracranial, or intraspinal event within 3 months. These intracerebral events specifically include stroke, arteriovenous malformations, neoplasm, aneurysm, cranial trauma, or surgery. Major trauma or surgery within 14 days, aortic dissection, and uncontrolled hypertension also represent exclusion criteria. Additional exclusion criteria are a known bleeding disorder, prolonged cardiopulmonary resuscitation with thoracic trauma, lumbar puncture within 7 days, and recent arterial puncture at a noncompressible site. For patients with a high risk of complications but who require aggressive intervention for pulmonary embolism and hemodynamic compromise, catheter-directed or surgical embolectomy may be considered.


Further Reading


TOLL-LIKE RECEPTORS

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Abstract

Toll-like receptors (TLRs) are members of the IL-1 receptor superfamily, and comprise a family of molecules that detect and facilitate responses to a broad range of bacterial and viral pathogens. Additional roles for these receptors in disease may include the detection of tissue damage at inflammatory sites. Genetic defects in TLR signaling pathways confirm their importance in controlling infections, and are associated with reduced risks of inflammatory diseases. TLR agonists exert powerful adjuvant effects, and are providing new treatments to enhance vaccine efficiency and desensitize allergic inflammation. TLR antagonists may also be useful anti-inflammatory treatments in established disease.

Introduction

First described because of its role in fly development, conditional Toll mutants demonstrated a role for the Toll protein in fly immunity. The family of Toll-like receptors have become the subject of intense interest following the realization that they provide vital mechanisms allowing cells (immunological and non-immunological) to detect and respond to both pathogens and endogenous signals of tissue damage. Two groups showed that mice resistant to the effects of bacterial endotoxin had defects in a mammalian homolog of Toll, named Toll-like receptor (TLR) 4, providing the identity of the long-sought-after signaling protein enabling responses to endotoxin. TLRs comprise a large family (10 proteins in man, 11 in mouse). For most of these, evidence of an important role in host defense is accruing. Their enormous potential to alter patterns of sensitization and subsequent T-cell-driven responses has stimulated intense interest, and new therapeutic agents exploiting TLRs are already in clinical trials.

Structure

TLRs are members of the IL-1R superfamily. Homology with the IL-1R resides in the intracellular regions involved in signaling. In particular, the receptors all possess the intracellular Toll/interleukin receptor (TIR) domain, which is crucial for signaling. Three regions within the TIR domain have been defined in receptor mutagenesis studies (principally of the type 1 IL-1R, but also of TLR2 and TLR4) that are of particular importance. Of these ‘boxes’, box 1 and box 2 are vital to signaling, and box 3 to cell surface expression. The TIR domain is also a feature of a family of adapter molecules, which associate with activated TLRs through TIR domain-mediated interactions and create the early signaling complexes. Dominant negative molecules that prevent TLR signaling can be readily created by point mutations (typically of a highly conserved proline residue within box 2) in either the TLRs or signaling adapters, emphasizing the crucial nature of this region of the molecule. The extracellular portions of the TLRs are characterized by leucine-rich repeat motifs, which are thought to be involved in ligand