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CHAPTER

THROMBOLYTIC CONSIDERATIONS WHEN USED WITH ANTICOAGULANTS

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INTRODUCTION

Today thrombolytic agents such as recombinant tissue plasminogen activator (rt-PA), reteplase, and tenecteplase (TNK) are crucial agents in the treatment of acute myocardial infarction (AMI), stroke, venous thromboembolism (VTE) (including massive pulmonary embolism [PE]), and peripheral arterial thrombosis as well as other unique thromboembolic conditions. Their ability to dissolve clot, as opposed to preventing clot expansion, is a key distinguishing characteristic from other anticoagulant agents, which makes them valuable options when immediate nonsurgical reperfusion of an occluded vessel is warranted. Despite their clinical utility, thrombolytic agents carry a high risk of bleeding, especially intracranial hemorrhage. Patient selection must be carefully considered to optimize the risk–benefit ratio with these agents.

PHARMACOLOGY AND PHARMACOKINETICS[1-9]

- Four thrombolytic agents are commercially available in the US: streptokinase, rt-PA (alteplase [Activase]), reteplase (Retavase), and TNK (TNKase). Each of these agents has distinct pharmacologic properties that impact their clinical use (see **Table 6-1**).

Mechanism of Action

- All of the available agents exert their effect on the endogenous fibrinolytic system by converting plasminogen to plasmin through hydrolysis of the arginine–valine bond in plasminogen. Plasmin cleaves fibrin and fibrinogen leading to clot dissolution, as well as degrading the procoagulant factors V and VIII.
- Urokinase and streptokinase produce plasminogen activation on a systemic level, leading to global activation of plasminogen to plasmin. With doses used for systemic effects, plasmin may be depleted and fibrin/fibrinogen degradation products may produce a systemic anticoagulant effect.
- Recombinant t-PA, reteplase, and TNK are all fibrin-specific thrombolytic agents. As such, minimal amounts of plasminogen are converted to plasmin in the absence of fibrin leading to a more localized thrombolytic effect.

- Of note, in patients with plasminogen levels significantly below normal (e.g., <50%) at therapy initiation, the therapeutic response from an exogenously administered thrombolytic agent may be blunted or less than expected.
- Thromboelastography (See Chapter 21, Coagulation Laboratory Considerations) can be used to assess the level and duration of thrombolysis. It can be a useful tool to determine if adequate lysis is present when attempting to dissolve a thrombus, but cannot be used to determine if thrombolytic dosage is too high.

Pharmacologic and Clinical Properties of Thrombolytics

TABLE 6-1: **Characteristics of Available Thrombolytic Agents**

Property	Urokinase+	Streptokinase	Alteplase (rt-PA)	Reteplase	Tenecteplase (TNK)
Molecular weight, kD	35	47	70	39	70
Half-life, min	13–20	23	4–8	14–18	23–37
Fibrin specificity	Minimal	Minimal	Moderate	Moderate	High
Potential antigenicity	No	Yes	No	No	No
Plasminogen binding	Direct	Indirect	Direct	Direct	Direct
FDA-approved indications	PE	MI, PE, DVT	MI, PE, stroke, catheter occlusion	MI	MI
Patency with TIMI Grade 3 flow* – 90 min	NA	40–50%	46–75%	60–63%	63%

+Currently not commercially available in the United States.

*TIMI Grade 3 flow (see Table 6-3): complete perfusion defined by normal flow, which fills the distal coronary bed completely. TIMI Grade 0 flow is no perfusion, with Grades 1 and 2 representing partial perfusion of the myocardium.

DVT: deep venous thrombosis, FDA: U.S. Food and Drug Administration, MI: myocardial infarction, PE: pulmonary embolism, TIMI: thrombolysis in myocardial infarction

INDICATIONS, DOSING, AND ADMINISTRATION[10-44]

- Depending on the half-life of the compound being used, administration is either by single or multiple intravenous (IV) boluses or through a continuous IV infusion given for a specified time frame (see **Table 6-2**).
- Catheter flush is for localized (catheter-related) thrombosis.
- Devices (e.g., ultrasound-accelerated thrombolysis catheters, mechanical circulatory support).