Toxin-induced Coagulopathy

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KEYWORDS

• Oral anticoagulation • Prothrombin complex concentrates
• Direct thrombin inhibitors • Xa antagonists • Platelets

KEY POINTS

- New oral anticoagulation drugs now target specific components in the coagulation cascade.
- Vitamin K and fresh frozen plasma remain mainstays of treatment of minor bleeding from vitamin K antagonists.
- Prothrombin complex concentrates are available in 3- and 4-factor forms that have shown improved safety and efficacy when used to reverse bleeding from vitamin K antagonists and promise when used for the reversal of the new direct thrombin inhibitors and Xa inhibitors.

INTRODUCTION

Since their discovery in the early nineteenth century, anticoagulants have been a mainstay of treatment of venous thromboembolism (VTE) and pulmonary embolism (PE). Anticoagulation has also become a major arm of treatment for prevention of procoagulant states in patients with diseases ranging from atrial fibrillation to lupus to a myriad of genetic mutations that subject patients to clotting. Until recently, the choice of anticoagulation in patients who require it has remained relatively simple, because aspirin, heparins, and warfarin were the mainstay of treatment. In the early 2000s, new, potent anticoagulants were developed and brought to market. Increasingly, patients on the "new anticoagulants" are presenting to emergency departments (EDs) either with complications and toxicity from these new drugs, and it has become important for the emergency practitioners (EPs) to be aware of their potential complications. This article reviews the toxicity of anticoagulant drugs and suggests strategies for treating overdose and complications.

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BACKGROUND

The Coagulation Cascade

In the setting of injury or inflammation to blood vessels, the activation of the coagulation cascade attempts to achieve hemostasis and prevent bleeding. Injury to the endothelium of blood vessels exposes tissue factor and fibrinogen, which activate platelets in the primary hemostatic pathway.[1] Fibrinogen binds von Willebrand factor (vWF) on platelets and to induce aggregation. A myriad of other receptors on platelets contributes to this process, the most common of which is glycoprotein IIb/IIIa. Activated platelets bind to collagen exposed from endothelial damage.

Secondary hemostasis involves the three classic clotting cascades, the intrinsic, extrinsic, and common pathways.[1] The endpoint of coagulation is to convert soluble fibrinogen to fibrin, which provides the scaffolding for a platelet aggregate, allowing for a stable clot. The intrinsic pathway begins with binding of factor XII on exposed collagen from damaged tissue, in turn causing a cascade of activation of multiple other coagulation factors that drive the conversion of fibrinogen to fibrin. Simultaneously, the extrinsic clotting cascade is activated in the presence of tissue factor. Tissue factor attracts inactive factors X, V, and VII that are bound to cell membranes and activates them, converting prothrombin to thrombin. Thrombin provides positive feedback in the extrinsic pathway, activating more factors that in turn create more thrombin. The two pathways unite in the common pathway that will produce a strong fibrin clot with platelets that provides hemostasis. A variety of anticoagulation drugs take advantage of this cascade to target specific clotting factors, resulting in cessation of the coagulation cascade at specific points during the process (**Fig. 1**).

Measures of Anticoagulation

Simple laboratory tests can assess the activity of the intrinsic and extrinsic coagulation cascade. The activated partial thromboplastin time (aPTT) is a standard measurement of the intrinsic clotting cascade. Reference ranges depend on laboratories but typically are between 30 and 50 seconds. Activity of factors I, II, V, VIII, IX, X, XI, and XII must be present to have a normal aPTT. Notably, the presence of tissue factor is not included in this reaction and, as a result, the test is termed “partial.” Deficiencies

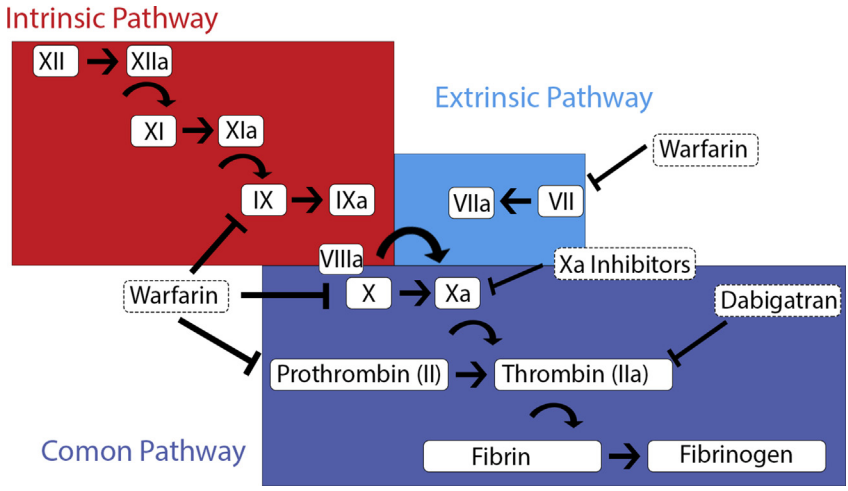

Fig. 1. Intrinsic, extrinsic, and common coagulation pathways.