Anticoagulant Reversal and Anesthetic Considerations

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KEYWORDS

• Laboratory monitoring • Prothrombin complex concentrates
• Specific reversal agents • Factor Xa inhibitors • Direct thrombin inhibitors

KEY POINTS

- Bleeding complications are a common concern with the use of anticoagulant agents. In many situations, reversing of neutralizing their effects may be warranted.
- Prothrombin complex concentrate (PCC) replaces coagulation factors lowered by warfarin, as does fresh frozen plasma (FFP), but in a more concentrated form.
- Protamine negates the effect of heparin and combines chemically with heparin molecules to form an inactive salt. It also partially reverses the effects of low-molecular-weight heparin (LMWH).
- Recombinant activated factor VII is a nonspecific procoagulant that activates the extrinsic clotting pathway resulting in thrombin generation but does not directly neutralize the activity of any of the new oral anticoagulants.
- Dabigatran etexilate is an oral direct thrombin inhibitor (DTI) that can be reversed with both PCC and idarucizumab.
- Rivaroxaban, apixaban, and edoxaban are all oral factor Xa inhibitors that can be reversed with PCC, andexanet alfa, and cirapirantag.

INTRODUCTION

Anticoagulants are an important part of the treatment of many disease processes, including atrial fibrillation,[1] venous thromboembolism (VTE),[2] arterial thromboembolism (ATE),[3] and intrinsic hypercoagulable states. They also play a key role in various surgical procedures, such as cardiac and vascular surgeries, as well as percutaneous catheter-based interventions. These agents cause an appreciable increase, however, in the risk of spontaneous hemorrhage[4] and a decrement in hemostasis, as seen in

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higher transfusion requirements during surgery.[5] Understanding the pharmacokinetics and clinical effect of these agents as well as effective strategies for anticoagulant reversal is key for effective and safe provision of anesthesia, especially in emergencies.

AVAILABLE AGENTS

A wide variety of anticoagulant agents are available (**Table 1**). These agents have various mechanisms of action (**Figure 1**), duration of effect, and method of reversal.

HEPARINS

Heparins are naturally occurring glycosaminoglycans.[19] Their native function is at this time unproved. Heparins are commonly used for both treatment and prevention of thrombosis due to their ability to bind antithrombin III (ATIII) and thereby inhibit function of factor Xa and thrombin (factor IIa) as well as factors IXa, XIa, and XIIa.[20] Thrombin inhibition requires the heparin molecule to simultaneously bind ATIII and thrombin. LMWHs are too small to bind ATIII and thrombin simultaneously and are far more specific for inhibition of Xa.[19]

Heparins are typically isolated from bovine or porcine sources. It is thought that porcine heparins are safer due to a lower risk of heparin-induced thrombocytopenia (HIT), an immune-mediated disorder.[21] Unfractionated heparin is a mix of heparins of varying molecular weights, ranging in size from 3000 Da to 30,000 Da, with the molecule having an average mass of 15,000 Da.[19] Heparin activity is classically monitored by activated partial thromboplastin time (aPTT), although the evidence for this is poor and therapeutic ranges must be institution specific due to variability in test reagents and protocols.[22]

LMWHs, such as enoxaparin, are purified to select out smaller molecules, typically of 4000 Da to 9000 Da. These smaller molecules are more specific for Xa inhibition,[23] have more reliable pharmacokinetics,[24] and carry a lower risk of HIT.[25] Fondaparinux is a synthetic pentasaccharide that preserves the ATIII-binding domain of heparin, preserving the active site.[26] Like LMWH, fondaparinux has more predictable kinetics and is more selective for activity against factor Xa. Routine monitoring of LMWHs is not recommended. If necessary, anti-Xa activity should be assayed.

Indications

Heparin is indicated for a wide variety of conditions. Subcutaneous heparin, either unfractionated or LMWH, is frequently administered to hospitalized patients for the prevention of VTE.[2] Intravenous unfractionated heparin, most commonly as a continuous infusion, and subcutaneous LMWH are indicated for the treatment of VTE,[2] ATE,[3] and acute myocardial infarction. Bolus doses of unfractionated heparin are commonly given during cardiac and vascular surgeries as well as catheter-based interventions. Additionally, patients with mechanical prosthetic valves, ventricular assist devices (VADs), and on extracorporeal membrane oxygenation (ECMO) support must be maintained on systemic anticoagulation at all times for prevention of device thrombosis, and heparin is often used during bridging or hospitalization.[27]

Kinetics

Unfractionated heparin can be given either intravenously or subcutaneously. Intravenous heparin reaches peak effect within 3 minutes and has an elimination half-life of 1 hour to 1.5 hours.[28] Subcutaneous unfractionated heparin reaches peak effect