Anticoagulants
Pharmacokinetics, Mechanisms of Action, and Indications

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KEYWORDS

• Anticoagulation • Pharmacokinetics • Mechanism of action • Indication

KEY POINTS

- Patients presenting for elective as well as urgent neurosurgical procedures are commonly receiving anticoagulant therapy.
- Understanding how each anticoagulant agent exerts its activity and the indications for use is important for clinicians when initiating and managing anticoagulant therapy.
- Knowledge of fundamental pharmacokinetic profiles of anticoagulant drugs is necessary to help minimize bleeding and achieve optimal surgical outcomes.

INTRODUCTION

Patients requiring neurosurgical procedures, including elective and emergent surgery, are often receiving an anticoagulant for a non-neurosurgical indication, such as atrial fibrillation, venous thromboembolism, or a mechanical heart valve. To achieve optimal outcomes and minimize the risk of periprocedural bleeding, members of the neurosurgical team must understand and have a sound working knowledge of (1) anticoagulants currently used in patient care; (2) their pharmacokinetic effects, distribution, and potential for drug-drug interactions; and (3) approved clinical indications.

MECHANISM OF ACTION

Treatment options for anticoagulation have increased substantially over the past 10 years with the development and wide-scale availability of oral direct thrombin inhibitors and oral direct factor Xa inhibitors. The addition of these agents to an armamentarium of existing drugs administered intravenously, subcutaneously, or orally has expanded treatment options for thromboprophylaxis and targeted anticoagulation. Differences between these medication classes are summarized and shown in **Fig. 1**.

UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) is a desirable choice for anticoagulation when a rapid anticoagulant effect is needed due to its rapid onset of action when administered intravenously. UFH is a mixture of sulfated glycosaminoglycans of variable lengths and molecular weights. The anticoagulant effects and pharmacologic properties vary with the size of the molecules.[1,2] UFH exerts its anticoagulant effects in 3 distinct ways. The major anticoagulant effect is the result of its high affinity for antithrombin (AT) and the conformational change in

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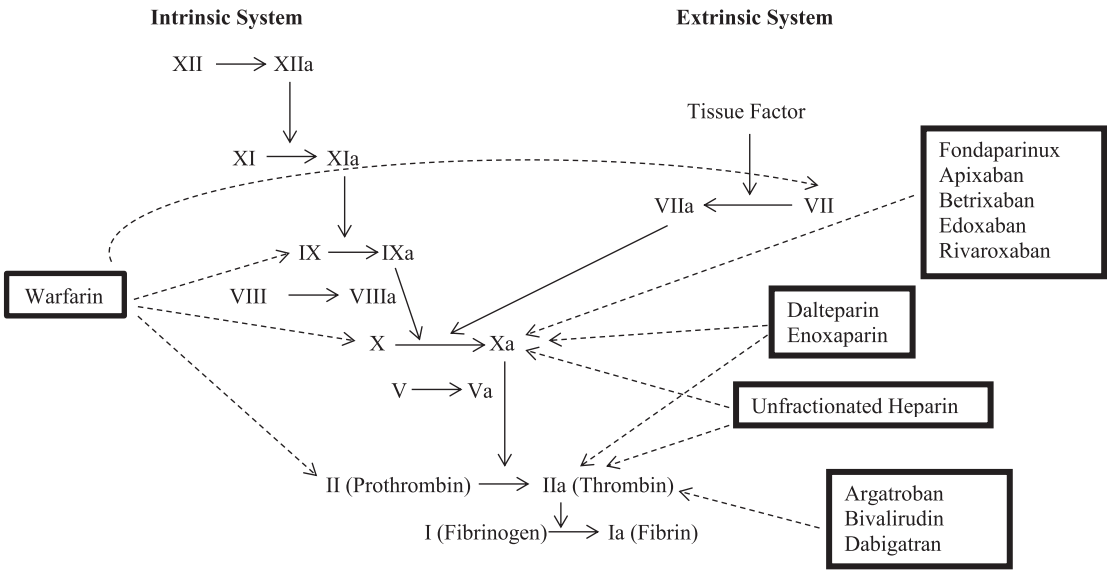

Fig. 1. Overview of coagulation cascade and primary site(s) of action for anticoagulant drugs.

antithrombin (AT) that results from their interaction of heparin and AT. This change accelerates the ability to inactivate the coagulation enzymes thrombin, factor IXa, factor Xa, factor XIa, and factor XIIa. Thrombin and factor Xa are most sensitive to inhibition by the heparin/AT complex; thrombin is approximately 10-fold more sensitive to the inhibiting effects than factor Xa.[1–3] Inhibition of thrombin by UFH requires binding to AT by means of a unique pentasaccharide segment of the heparin molecule and also simultaneous binding of heparin to thrombin by 13 additional saccharide units. Approximately one-third of UFH molecules contain the high-affinity pentasaccharide required for anticoagulant activity.[1,2] The second way in which UFH exerts an anticoagulant effect is through its activity as a catalyst to the inactivation of thrombin by heparin cofactor II. This anticoagulant effect is specific for thrombin and requires much higher doses of UFH than those required to catalyze AT activity.[2] The third anticoagulant effect of UFH is modulation of factor Xa generation, by heparin binding to factor IXa. This effect is not considered clinically significant because it requires dosing of heparin well above those needed for therapeutic efficacy and maintained safety.[1] UFH strongly inhibits thrombin in plasma; the heparin-AT complex is unable to inhibit thrombin bound to fibrin.[1,2]

LOW-MOLECULAR-WEIGHT HEPARINS

Low-molecular-weight heparins (LMWHs) are derived from UFH by means of chemical depolymerization.[1–3] The overall process creates fragments that are approximately one-third the molecular weight of UFH and are also heterogeneous in size.[3] The chemical modification changes several properties of LMWHs. Similar to UFH, LMWHs have a major role in catalyzing AT-mediated inhibition of coagulation factors. However, 50% to 75% of LMWH chains are too short and they experience a progressive loss of ability to catalyze thrombin inhibition.[3,4] These chains, however, are capable of promoting factor Xa inhibition, ultimately leaving LMWHs as more selective inhibitors of factor Xa than UFH.[3] Other distinguishing features of LMWHs from UFH include reduced protein binding that improves their pharmacokinetic properties and results in a more predictable anticoagulant response and reduced interaction with platelets, which results in a reduced formation of heparin-induced thrombocytopenia (HIT) antibodies and incidence of HIT.[3–6]

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors interact directly with thrombin; they do not require AT or heparin cofactor II to achieve an anticoagulant effect. They specifically and reversibly inhibit free and clot-bound thrombin by binding to the active site of thrombin.[7–9] Argatroban is classified as a univalent direct thrombin inhibitor, binding only to the catalytic (active) site of thrombin as a competitive inhibitor of thrombin. Bivalirudin is a bivalent thrombin inhibitor, binding to both the catalytic (active) site and the substrate recognition (exosite 1) site of thrombin molecule.[10] Inhibition of thrombin attenuates formation of fibrin, reduces thrombin generation, and may limit platelet activation and aggregation.[11–13] Dabigatran is the only oral direct thrombin inhibitor currently approved