

The Complex Clinical Picture of Side Effects to Anticoagulation

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KEYWORDS

• Adverse drug reaction • Coumarin • Heparin
• Hypersensitivity • Skin necrosis • Thrombocytopenia

Antithrombotics are used to prevent intravascular thrombus formation or dissolve blood clots by influencing the coagulation cascade, thrombolysis, or thrombocyte function. Accordingly, 3 main groups of substances are differentiated: anticoagulants (inhibiting fibrin formation), thrombolytic drugs (dissolving fibrin), and thrombocyte aggregation inhibitors.

Anticoagulants are used for prophylaxis and therapy for thromboembolic complications. According to the mechanism of action, direct anticoagulants interacting directly with coagulation factors such as heparins, heparinoids, hirudins, and thrombin inhibitors are distinguished from indirect anticoagulants, which interfere with the synthesis of clotting factors (vitamin K antagonists). Side effects of anticoagulants may be caused by predictable pharmacologic effects (type A reactions, a = augmented) or be caused by unpredictable events such as immune reactions and individual disposition (type B reactions, b = bizarre) (**Fig. 1**). Heparin is still the most commonly used anticoagulant for hospitalized patients but its usage has also increased in outpatient settings.¹ Cost pressure on hospitals has led to earlier discharge of patients or ambulatory surgeries so that side effects of heparin treatment are nowadays increasingly observed in outpatients.

Following a summary of the coagulation physiology and common anticoagulant drugs, the focus of this review is on the clinical appearance, diagnostics, and therapy for anticoagulant-induced type B reactions.

PHARMACOLOGY OF COAGULATION

According to current knowledge, blood coagulation does not simply consist of 2 converging cascades (intrinsic and extrinsic pathways) as previously believed but

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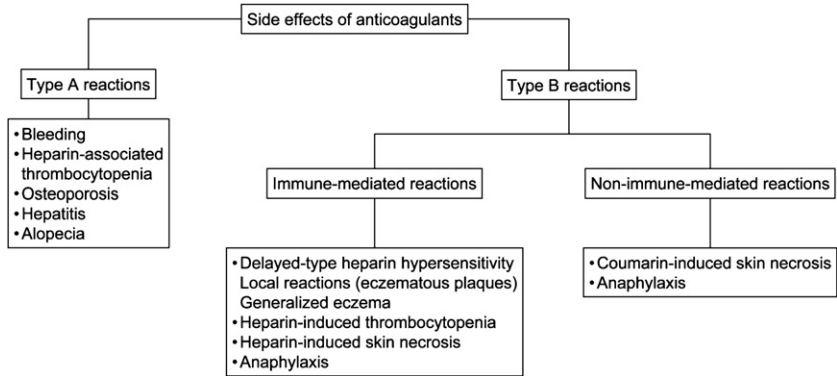


Fig. 1. Type A and type B reactions to anticoagulants.

rather is a chronology of 3 coagulation phases.² (1) In the initiation phase, injury of the endothelium leads to interaction of circulating active factor VII (FVIIa) with an endothelial cell-bound transmembrane glycoprotein (tissue factor [TF]) with formation of a catalytic complex (FVIIa/TF). This FVIIa/TF complex activates FX to FXa resulting in the production of small amounts of thrombin (FIIa). (2) In the amplification phase, thrombin itself promotes molecular and cellular changes for generation of greater thrombin amounts. (3) In the following propagation phase, thrombin efficiently binds to the surface of activated thrombocytes, which is followed by fibrin polymerization and development of stable fibrin clots.

Pharmacologic interference of coagulation principally aims to inhibit thrombin (FIIa), which is the key molecule of homeostasis. This aim may be achieved by interference with all coagulation phases or by inhibition of single clotting factors.³

Heparin

Heparins are naturally occurring polysaccharides that contain multiple carboxyl and sulfate groups. Their anticoagulation capacity depends on the anionic charge of these carboxyl and sulfate groups. High molecular weight and negative charge prevent resorption after oral administration and therefore parenteral application of heparins is mandatory. The crucial mechanism of action is the activation of antithrombin by binding to a specific pentasaccharide sequence of the heparin polymer.⁴ For thrombin inhibition it is essential that the heparin polymer consists of at least 18 monomers allowing formation of a complex of heparin, antithrombin, and thrombin. For inhibition of FXa only the pentasaccharide sequence is necessary. Therefore, unfractionated heparin (UFH) inhibits thrombin and FXa, whereas low-molecular-weight heparin (LMWH) exerts its anticoagulation effect mainly by blockade of FXa.

UFH

Pharmaceutical heparin preparations are extracted from porcine intestinal mucosa. During processing they are partially fractionated and depolymerized.⁵ Therefore, UFH preparations are not pure substances but a composite of heterogeneous molecules varying in size and chemical structure. For this reason, the dose of UFH is not recorded in milligrams but in international units (IU). The average molecular weight of UFH is 15 kDa corresponding to 40 to 50 monomers. Generally, long-chain heparins are eliminated faster than short-chain heparins. In addition, only 30% to 40% of UFH contain the specific pentasaccharide sequence that is responsible for the

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