

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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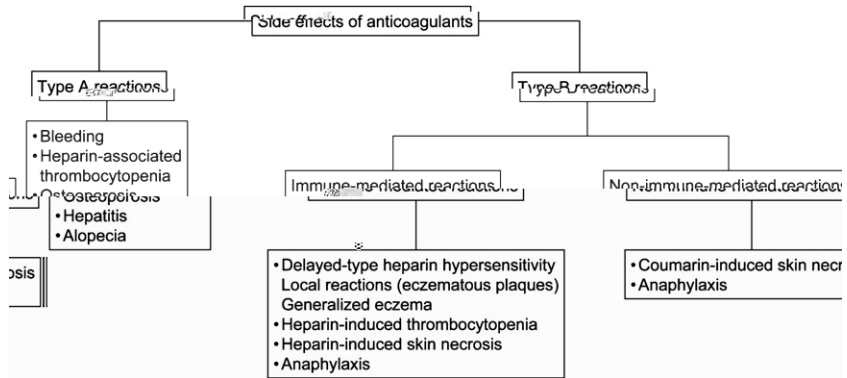


Fig. 1. Type A and type B reactions to anticoagulants.

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

These highly effective anticoagulants lead to inhibition of vitamin K-dependent coagulation factors (ie, FII, FVII, FIX, FX).¹² They are administered orally, metabolized by hepatic cytochrome enzymes (mainly isoform CYP2C9) and excreted as inactive metabolites into the bile. Disadvantages of vitamin K antagonists include delayed onset of action, narrow therapeutic index (bleeding complications) as well as numerous interactions with drugs and foods.

In summary, despite some progress, the therapeutic options for anticoagulation remain unsatisfactory. Compared with UFH, LMWH have several advantages but are chemically not clearly defined, act antithrombin-dependently, and have to be applied parenterally. Because of lack of antidotes for neutralization, application of direct thrombin inhibitors is always associated with increased risk of bleeding complications. Therefore, despite the development and approval of these new anticoagulants (direct thrombin inhibitors, FXa inhibitors), heparin remains the medication of first choice especially for intravenous anticoagulation.¹³ Current development of new anticoagulants is based on the improved understanding of coagulation physiology and is dominated by the search for orally active direct anticoagulants.^{3,14}

DELAYED-TYPE HEPARIN HYPERSENSITIVITY

In case of DTH to subcutaneously injected heparins, itchy erythematous or eczematous plaques develop around injection sites (Fig. 2A).¹⁵⁻²⁰ The usual latency for development of characteristic lesions during ongoing therapy is 7 to 10 days; in cases of previous sensitization and re-exposure, skin lesions appear within 1 to 3 days. The spectrum of skin lesions ranges from mild erythema with little infiltration to typical eczematous plaques with papulovesicles located on an infiltrated erythematous

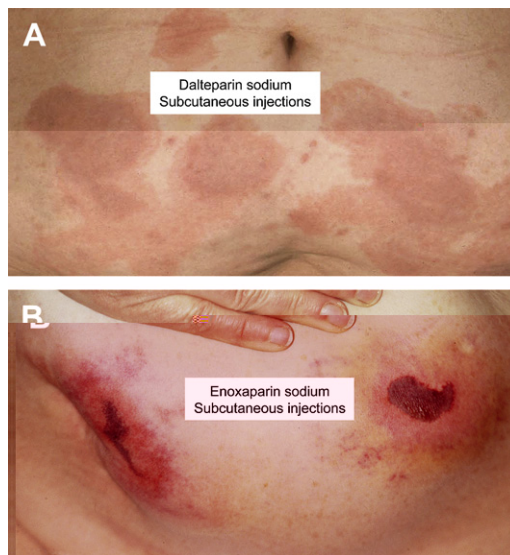


Fig. 2. DTH to subcutaneously applied heparins and heparin-induced skin necrosis. (A) Itchy erythematous and eczematous plaques 12 days after initiation of subcutaneously applied dalteparin. (B) Painful heparin-induced skin necrosis at injection sites 10 days after initiation of subcutaneous enoxaparin injections. (Reproduced from Gaigl Z, Klein CE, Großmann R et al. [Managing allergy to heparins]. *Dtsch Arztebl* 2006;103:2878 [in German]; with permission.)

ground. Less frequently, in cases with continuation of subcutaneous injections despite local reactions, a generalized eczema or exanthema with accentuation around injection sites may be observed.^{21–25} In early erythematous lesions, histopathologic examination reveals a dense mononuclear infiltrate of predominantly CD4⁺ lymphocytes with scattered eosinophils. Eczematous lesions additionally show epidermal spongiosis.^{15,18,22,26} These findings are consistent with an immunologically mediated DTH reaction of the skin. However, potential antigenic determinants of the heparin molecule have not yet been determined. DTH reactions to subcutaneously injected heparin are mostly described in obese women.^{27,28} Therefore, gender and obesity seem to be risk factors for the development of DTH to heparin. It is tempting to speculate that hormonal and metabolic influences may play a role in the pathogenesis.²⁹

The differential diagnosis of erythematous and eczematous plaques after subcutaneous heparin administration includes hematomas, local infections, and eczema caused by skin disinfectants.³⁰ However, the most important differential diagnosis is heparin-induced skin necrosis (**Table 1**).^{30,31} In most cases the allergologist does not see the lesions and the presumptive diagnosis relies on the description by referring physicians or patients. Moreover, nondermatologists and/or nonallergologists may confuse the clinically distinct signs of skin necrosis, that is, redness of the skin is assumed to be the same as eczema or dermatitis.

Allergologic Testing

Patients with suspected DTH to heparins should be subjected to an allergologic workup including skin tests and subcutaneous challenge tests. In cases in whom DTH to heparins is verified, intravenous challenge tests should be done (**Fig. 3**). The

Table 1
Comparison of heparin-induced DTH and HIT-associated skin necrosis

	DTH	HIT
Incidence	1%–5%	UFH: up to 3% LMWH: <0.1%
Latency	7–10 days (sensitization) 1–3 days (re-exposure)	5–14 d (sensitization) 3–5 d (re-exposure within 100 d)
Symptoms	Itching	Pain
Gross appearance	Erythema, plaque, eczema (dermatitis)	Necrosis, hemorrhagic rim
Histology	Dermal mononuclear infiltrate of lymphocytes, spongiosis	Thrombosis of skin vessels without signs of vasculitis
Associated features	None	Thromboembolic complications (white-clot syndrome)
Prognosis	Good	Poor, if thromboembolism occurs
Pathogenesis	T cell–mediated allergic hypersensitivity	Immune complexes composed of heparin, platelet factor 4, and specific IgG antibodies activating thrombocytes
Allergologic testing	Skin test, s.c. provocation, i.v. provocation	Contraindicated
Recommendations	Fondaparinux s.c. Heparin i.v. Topical steroids	Danaparoid, hirudins Re-exposure to heparins has to be avoided

Abbreviations: i.v., intravenous; s.c., subcutaneous.

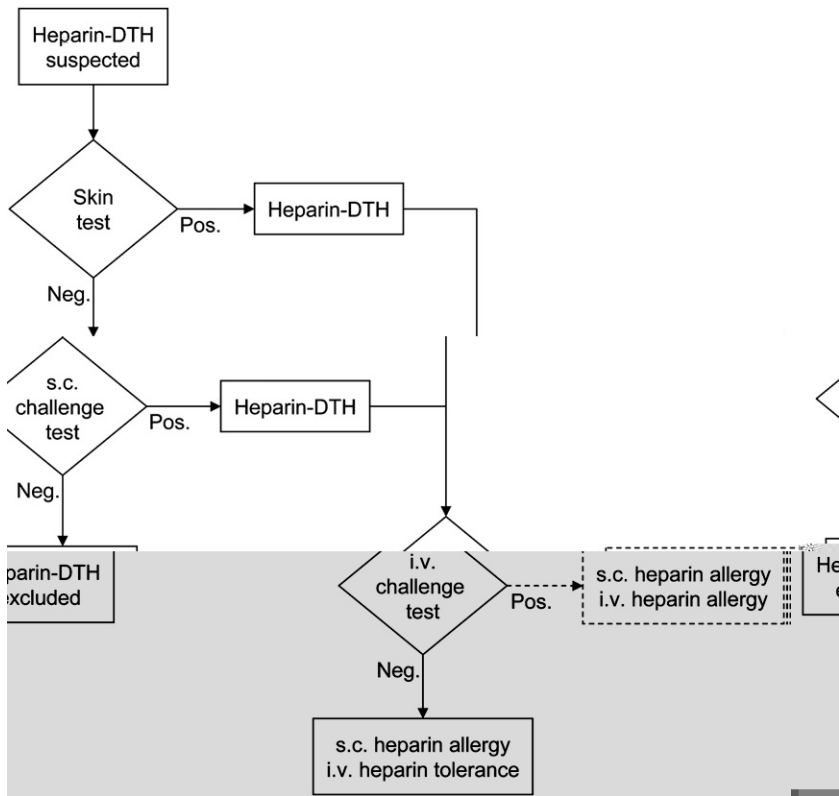


Fig. 3. Recommended steps of the allergologic workup in patients with a history of DTH to subcutaneously injected heparins. Diagnosis in case of a positive intravenous challenge test is depicted in dotted lines because this has not occurred in our studies where all patients tolerated intravenous challenge tests. i.v., intravenous; s.c., subcutaneous. (Reproduced from Trautmann A, Seitz CS. Heparin allergy: delayed-type non-IgE-mediated allergic hypersensitivity to subcutaneous heparin injection. *Immunol Allergy Clin N Am* 2009;29:473; with permission.)

authors perform intradermal tests on the volar forearm and patch tests on the upper back with a panel of heparin and heparinoid preparations, including an UFH, as well as LMWHs (nadroparin, dalteparin, and enoxaparin), heparinoids (danaparoid and pentosan polysulfate), and fondaparinux. Allergologic testing of patients with a panel of different heparin preparations reveals cross-reactivity among heparins and excludes a causal role of the preservatives sometimes added to heparin multidose products, such as sodium metabisulfite, benzyl alcohol, or chlorocresol. However, most single-dose heparin products contain salts, acids, or bases for pH adjustment, but no preservatives. As a rule, multiple positive reactions throughout the test panel of UFHs and LMWHs do reflect extensive cross-reactivity. Single negative skin test reactions are usually false-negative and subsequent subcutaneous challenge proves cross-reactivity.

Immediate-type reactions may be observed in approximately 10% of intradermal tests despite the 1:10 dilution of heparin solutions. These immediate wheal-and-flare responses are mainly caused by histamine liberation and contamination of the heparin

preparation and should therefore not be interpreted naively as proof of an IgE-mediated allergy. These unspecific histamine-mediated reactions may be discriminated from extremely rare allergic reactions by negative intradermal tests with further dilutions (1:100, 1:1000), whereas true allergic reactions still produce positive skin test results with these lower concentrations. Anaphylaxis symptoms and/or immediate-type skin test reactions may also be caused by accidental or deliberate contaminants (eg, oversulfated chondroitin sulfate [OSCS]) during the processing of heparins.^{32–34}

Subcutaneous Allergy and Intravenous Tolerance

In cases of DTH to subcutaneously injected heparin, intravenous application of this drug theoretically implies the risk of a generalized eczematous reaction. However, evidence that intravenous administration of heparin is tolerated despite DTH was previously observed in single patients.^{35–38} In 2 prospective studies, the authors showed that intravenous administration of heparin was well tolerated without side effects in 64 patients who developed eczema-like infiltrated plaques after subcutaneous injection of heparin.^{28,39} Therefore, intravenous application of heparin is a safe alternative for anticoagulation in these patients. Furthermore, in cases of therapeutic necessity, the shift from subcutaneous to intravenous heparin administration without previous tests may be justified even in cases with generalized eczema.²²

Currently it is unknown why some patients develop an immune reaction after subcutaneous application of UFH and LMWH, but still tolerate intravenous administration of UFH. Eczematous plaques after subcutaneously injected heparins are likely real DTH, caused by heparin-specific T lymphocytes. Subtle differences in the absorption of heparin from the skin and differential processing/presentation of antigens depending on the route of application may be responsible factors.

Cross-reactivity and Alternative Anticoagulation

Typical for DTH against subcutaneously administered heparins is the extensive cross-reactivity among all UFH and LMWH. Potential alternative antithrombotic compounds are the heparinoids, danaparoid and pentosan polysulfate.⁴⁰ Heparinoids were initially developed as alternatives in case of antibody-mediated HIT. Although danaparoid shows a low cross-reactivity with heparin in terms of heparin-induced antibody binding, it often cross reacts with heparin in case of DTH. Tolerance of a single subcutaneous challenge test should not be over interpreted. Several of our patients developed eczematous plaques around injection sites despite an initial negative subcutaneous challenge test to heparinoids after a longer anticoagulation period and increasing number of heparinoid injections. As already suggested by the chemical structure, cross-reactivity between heparinoids and heparins is common.²⁶

Fondaparinux has been considered as a potential alternative anticoagulant compound.^{41,42} However, in 1 of our studies we observed positive skin tests with fondaparinux in 6 out of 16 patients with DTH to subcutaneously applied heparins. Meanwhile several studies confirmed that only up to 50% of patients with DTH to subcutaneous heparins tolerate fondaparinux.^{43–46} This is not surprising because fondaparinux is an anionic polysaccharide like heparin and therefore cross-reactivity may develop after continued anticoagulation for a longer period of time despite initial tolerance of the compound in skin and subcutaneous challenge tests.

HIT

Nonimmune-mediated thrombocytopenia is a common side effect of heparin treatment, occurring in up to 25% of patients. It is clinically characterized by a minor decrease of

thrombocytes (<30%) within the first 2 days of treatment.⁴⁷

anaphylactoid reaction). Evidence for IgE- or IgG-mediated allergic anaphylaxis to anticoagulants such as heparin and lepirudin is rarely reported in the literature. One case report suggests IgE-mediated allergy to subcutaneously administered dalteparin.⁶³ Such reactions to heparin preparations were also attributed to preservatives and protein contaminants of animal origin during the production process.⁶⁴ Minutes after initiation of intravenous lepirudin application, anaphylactic reactions with erythema, urticaria, angioedema, bronchospasm, laryngeal edema, hypotension, shock, and cardiorespiratory arrest were described. In 2 patients with anaphylaxis symptoms, lepirudin-specific IgG antibodies could be detected.^{65–67}

On the other hand, symptoms of nonallergic anaphylaxis may be caused by direct histamine release from mast cells and basophils by nonspecific binding of contaminants on membrane receptors or indirectly by complement/kinin activation. At the beginning of 2008 the Centers for Disease Control and Prevention registered a cluster of heparin-associated anaphylaxis reactions. Among patients receiving UFH during hemodialysis, reactions included dyspnoea, facial edema, urticaria, nausea or vomiting, tachycardia and hypotension, and life-threatening shock. In test samples of 1 heparin manufacturer, spectroscopy identified OSCS as well as dermatan sulfate, a known contaminant of heparin.³² Although chondroitin sulfate is a natural substance derived from animal cartilage, its oversulfated form (OSCS) does not occur naturally. OSCS exerts its effects by activation of the kinin-kallikrein system leading to generation of bradykinin, and activation of C3a and C5a, which are potent anaphylatoxins.^{34,68} The contaminated heparin could be traced back to China, where heparins are regularly processed by small, often unregistered plants. However, until now, it was not clear where the contamination occurred.

COUMARIN-INDUCED SKIN NECROSIS

Coumarin-induced skin necrosis is a rare (0.01%–0.1% of treated patients) complication of anticoagulant therapy with coumarin and its derivatives (phenprocoumon, warfarin/coumadin, and acenocoumarol) associated with significant morbidity and even mortality.^{69–71} Predilection sites of coumarin necrosis are areas of increased subcutaneous fat tissue such as breasts, abdomen, thighs, and buttocks.⁷² Typically, coumarin-induced skin necrosis develops in middle-aged women symmetrically within the first week of coumarin therapy (range 1–10 days); severe lesions appear between the third and sixth day. The first symptoms of coumarin-induced skin necrosis are paresthesia and circumscribed, livedo-like livid maculae coalescing into large hemorrhagic lesions with secondary blister formation. Within days these skin lesions become necrotic and deep painful ulcerations develop.

Coumarin-induced skin necrosis may occur because of a hereditary defect or in patients with acquired and transient protein C and/or S deficiency.^{73,74} Chronic liver disease, chronic renal failure and dialysis, acute leukemia, autoimmune diseases (lupus, antiphospholipid syndrome), infections (Epstein-Barr virus), acute respiratory distress syndrome, and plasmapheresis are all conditions with acquired protein C deficiency. Coumarin not only inhibits the synthesis and functional activity of the vitamin K-dependent clotting factors FII, FVII, FIX and FX but it also inhibits the anticoagulant proteins C and S. Protein C is an endogenous vitamin K-dependent anticoagulant, which decreases at the initiation of coumarin therapy faster (6–8 hours) than other coagulation factors (2–5 days). Especially in patients with protein C deficiency or initial high doses of coumarins, this disequilibrium results in temporary hypercoagulability leading to thrombotic occlusions of the microvasculature with consecutive skin necrosis. Coumarin necrosis is a severe but self-limiting local complication that slowly

resolves within several weeks but sometimes requires surgical debridement. Replace-

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