Adverse Drug Reactions and Cutaneous Manifestations Associated With Anticoagulation

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Abstract

Anticoagulants are amongst the most commonly prescribed medications worldwide. Although rare, localised and systemic drug reactions have been reported with anticoagulants that can lead to significant morbidity and mortality. Some of the first signs of drug reactions to anticoagulants are cutaneous changes that, when recognised early, can prevent significant complications. Dermatologists should be aware of these changes to make an early and accurate diagnosis. This is particularly important in instances of skin-induced necrosis caused by systemic toxicity to anticoagulants. This review discusses adverse drug reactions to the traditional anticoagulants, warfarin and heparin, and the newer direct oral anticoagulants (DOACs) such as the thrombin inhibitor, dabigatran, and the factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban. In particular, this review provides dermatologists with a framework for early diagnosis and management of patients with drug reactions to anticoagulants and alerts them to potential bleeding complications associated with minor procedures.

Anticoagulants are amongst the most commonly prescribed drugs worldwide.[1] Although haemorrhage is the most common and worrisome side effect, drug reactions to anticoagulants can also cause significant morbidity and mortality.[2,3] The prevalence of drug reactions is estimated to be between 0.01% and 7.5%.[3-5] These values vary depending on the type of anticoagulant, but overall, these numbers are likely an underestimation, since many physicians are only aware of bleeding complications. Unlike haemorrhage, many drug reactions to anticoagulant therapies have cutaneous manifestations that, when recognised early, can lead to timely management and treatment of symptoms.

Warfarin and heparin have been the mainstay of anticoagulant therapy for decades, whereas the direct oral anticoagulants (DOACs) have only been available for the past few years.[1,6,7] DOACs are small-molecule inhibitors that inhibit key proteins in the coagulation cascade and include dabigatran, which targets thrombin, and rivaroxaban, edoxaban, and apixaban, which target factor (F) Xa.[7-10] The DOACs are an improvement over both warfarin and heparin because they have better pharmacokinetics, have a more predictable anticoagulation profile, and do not require frequent laboratory monitoring.[7]

Several important drug reactions have been characterised for warfarin and heparin. Urticaria, morbilliform eruptions, skin necrosis, and purple toe syndrome are some of the most commonly reported drug reactions to warfarin.[11-13] Likewise, hypersensitivity and skin necrosis are also reported for patients on heparin and its derivatives.[4,5,14] Several case reports have documented drug eruptions, vasculitis, and angioedema as some of the more significant cutaneous side effects to DOACs. Due to the advantages over warfarin and heparin, the utility of DOACs is poised to rise, and over time more adverse drug reactions to these therapies will become apparent. Early recognition of drug reactions to anticoagulation is critical, as some of the more severe adverse events can lead to limb ischemia, amputation, or death.[4,5,11-13]

The aim of this review is to highlight the cutaneous manifestations and adverse drug reactions associated with anticoagulants and to alert dermatologists so they may provide timely and accurate diagnosis and management. The knowledge of the newer DOAC agents is also important for dermatologists who may perform minor procedures in the office to reduce the chances of bleeding complications.

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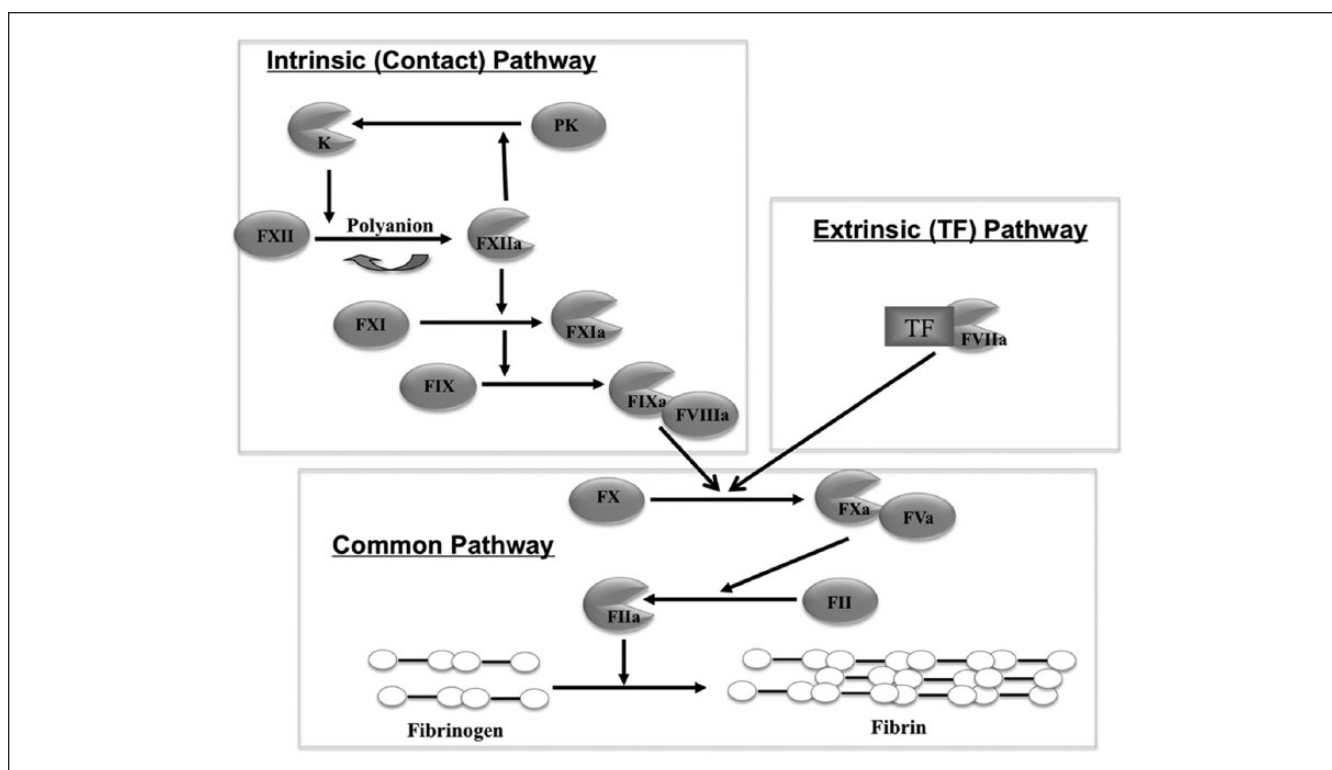Email: trang.vu@mail.utoronto.ca

Figure 1. The coagulation cascade. Coagulation is initiated by the intrinsic (contact) or extrinsic (tissue factor [TF]) pathway. In the intrinsic pathway, binding of FXII to polyanions triggers an autoactivation step, whereby small amounts of FXIIa are generated. FXIIa activates prekallikrein (PK) to kallikrein (K), which results in an amplification step whereby K feedback activates FXII to FXIIa. FXIIa then activates FXI to FXIa, and once generated, FXIa activates FIX to FIXa. Together, the protease FIXa and its cofactor FVIIIa form the intrinsic tenase complex, which activates FX to FXa.[15,16] TF is a transmembrane protein normally located in the subendothelial layer of the vessel wall but is exposed to the blood at sites of vascular injury or atherosclerotic plaque rupture. In the extrinsic pathway, exposed TF (cofactor) binds circulating FVIIa (protease) and forms the extrinsic tenase complex.[17,18] Both intrinsic and extrinsic pathways lead to the common pathway, whereby FXa is generated. The protease FXa binds its cofactor FVa to form the prothrombinase complex, which catalyses the activation of prothrombin (FII) into thrombin (FIIa). Thrombin cleaves fibrinogen, converting it into fibrin monomers that self-assemble to form a fibrin clot. Once generated, thrombin can feedback activate coagulation by activating FV, FVIII, and FXI to augment the procoagulant response. Thrombin also activates platelets to reinforce the clot.[16,18]

Overview of Coagulation and Anticoagulation

Coagulation is regulated by a series of enzymatic reactions that can be activated by the extrinsic or intrinsic pathway (Figure 1). Both pathways converge at the common pathway, which culminates in the formation of the protease, thrombin. Thrombin cleaves soluble fibrinogen into fibrin, which spontaneously self-assembles to form a fibrin meshwork that stabilises the platelet plug at sites of injury (Figure 1).[15-18] Several endogenous anticoagulant pathways exist to oppose the procoagulant response. Of note is the protein C (PC) and protein S (PS) pathway, as well as the serine protease inhibitor antithrombin (AT).[19,20]

Pharmacological anticoagulants work by disrupting either the procoagulant or anticoagulant pathways (Table 1). Warfarin interferes with the vitamin K–dependent carboxylation of a glutamate residue on the procoagulant proteins prothrombin, FVII, FIX, and FX and the anticoagulant proteins

PC and PS.[2,21] In contrast, heparin and its derivatives accelerate the anticoagulant activity of AT and, in doing so, impede clotting (Figure 2).[22-25] The DOACs directly inhibit the activity of key coagulation proteins such as thrombin and FXa.[7,10,26-30]

The clinical indications for anticoagulation, the mechanism of action of the drugs, their routes of administration, and reversal agents are summarised in Table 1. The following section describes the drug reactions associated with anticoagulation and their cutaneous manifestations (summarised in Table 2).

Drug Reactions to Warfarin

Warfarin-Induced Skin Necrosis

Warfarin-induced skin necrosis (WISN) affects between 0.01% and 0.1% of patients on warfarin, and to date, over 200 cases have been reported worldwide.[31,32] WISN is a condition

Table 1. Summary of Commonly Prescribed Anticoagulants, Their Clinical Indications, Route of Administration, Mechanism of Action, and Their Reversal Agents.

Anticoagulant	Clinical Indications	Administration	Mechanism of Action	Reversal Agent	References
Warfarin	• VTE (DVT and PE) • Thromboembolic prophylaxis in patients with prosthetic heart valves, AF, and MI	Oral	Inhibits γ-carboxylation of the Gla-region on FII, FVII, FIX, FX, PC, PS	Vitamin K	2, 21
UFH	• VTE (DVT and PE) • ACS • MI post-thrombolytic therapy	IV or SC	Accelerates AT inhibition of thrombin and FXa	Protamine sulphate	23-25
LMWH	• VTE (DVT and PE) • Thromboprophylaxis in general and orthopedic surgery • ACS	SC	Accelerates AT inhibition of FXa > thrombin[a]	Protamine sulphate	23-25
Pentasaccharides	• VTE (DVT and PE) • Thromboprophylaxis in orthopedic surgery	SC	Accelerates AT inhibition of FXa	Recombinant FVIIa	25
Rivaroxaban (Xarelto)	• VTE (DVT and PE) • Thromboembolic prophylaxis in NVAF and orthopedic surgery	Oral	Inhibits FXa	In development	26-28
Apixaban (Eliquis)	• VTE (DVT and PE) • Thromboembolic prophylaxis of NVAF and orthopedic surgery	Oral	Inhibits FXa	In development	26-28
Edoxaban (Savaysa, Lixiana)	• VTE (DVT and PE) • Thromboembolic prophylaxis of NVAF and orthopedic surgery	Oral	Inhibits FXa	In development	10, 30
Dabigatran (Pradax, Pradaxa)	• VTE (DVT and PE) • Thromboembolic prophylaxis of NVAF	Oral	Inhibits thrombin	Idarucizumab	26, 27, 29

ACS, acute coronary syndromes; AF, atrial fibrillation; AT, antithrombin; DVT, deep vein thrombosis; Gla, vitamin K–dependent carboxylation/gamma-carboxyglutamic; IV, intravenous; LMWH, low molecular weight heparin; MI, myocardial infarction; NVAF, nonvalvular atrial fibrillation; PC, protein C; PE, pulmonary embolism; PS, protein S; SC, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolism.
[a]LMWH inhibits both FXa and thrombin but has greater inhibitory activity against FXa.

in which there is paradoxical formation of occlusive thrombi, leading to skin necrosis.[13,33] Although the precise mechanism leading to warfarin-induced hypercoagulability is unknown, it is thought to be due to the inhibition of the vitamin K–dependent proteins and their half-lives. The half-lives of FVII and PC are 5 and 8 hours, respectively, whereas the half-lives of coagulation factors II, IX, and X and the anticoagulant protein PS are 24 to 72 hours. Therefore, warfarin transiently induces an imbalance in the anticoagulant and procoagulant pathways, leading to thrombosis, and this is the leading theory.[13,33] However, WISN has been described in different clinical settings and has been observed in those starting warfarin therapy, those on maintenance therapy, and those who have ceased warfarin therapy for several days. Due to the variability in the clinical presentations, it is challenging to fully elucidate the pathogenesis of WISN.[13]

WISN often affects fatty regions of the body such as the breasts, abdomen, hips, buttocks, and thighs. The onset usually occurs within the first 3 to 8 days of therapy, albeit some patients developed symptoms within hours, or even months, after commencing warfarin.[2,33] Patients typically present with petechiae that can progress to ecchymosis and

haemorrhagic bullae. Associated symptoms include pain, paresthesia, or a sensation of pressure in the affected areas.[4,5,34] These signs and symptoms often present within the first 24 hours. Ultimately, the condition can progress to complete skin necrosis that infiltrates deep into the subcutaneous fat and can lead to infection, sepsis, or death.[33,34] A skin biopsy shows characteristic histopathological features, including the paradoxical presence of fibrin-containing microthrombi diffusely in the dermal and subcutaneous capillaries, venules, and deep veins. Endothelial cell damage, ischemic skin necrosis, and red blood cell extravasation are also histologic hallmarks that distinguish this entity from vasculitis.[13,34] A combination of the clinical history of anticoagulation, cutaneous manifestations, and a high index of suspicion can lead to timely management. Management involves warfarin cessation and switching to another anticoagulant such as the thrombin inhibitor, dabigatran.[35] In many cases, surgical intervention involving debridement, skin grafting, or amputation is also required.[34]

Several predisposing risk factors for WISN have emerged that may increase one's index of suspicion: (a) a high warfarin loading dose (>10 mg),[36] (b) female sex and obesity,[4,5,34] and
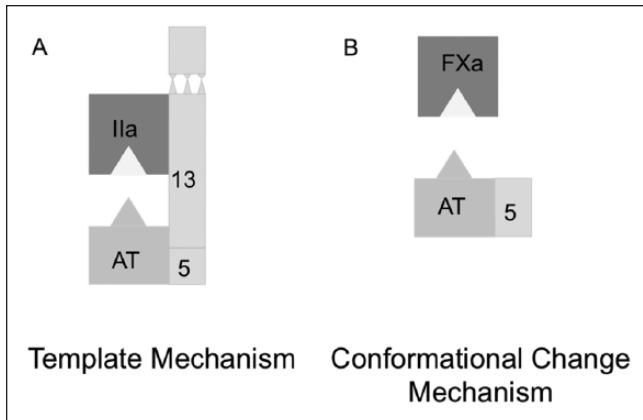
Figure 2. Mechanism of thrombin and FXa inhibition by the antithrombin (AT)–heparin complex. AT irreversibly inhibits the proteolytic activity of thrombin and FXa. Heparin molecules containing a unique pentasaccharide region can bind AT to induce a conformation change that significantly augments its inhibitory activity.[22-25] (A) The heparin-AT complex inhibits thrombin via a template mechanism. Heparin molecules with a pentasaccharide region and a total chain length of at least 18 saccharide units long are necessary to effectively bridge AT to thrombin, thereby facilitating inhibition. (B) In contrast, the presence of the pentasaccharide unit is sufficient for AT to inhibit FXa via a conformation change mechanism. Compared with unfractionated heparin (UFH), low molecular weight heparin (LMWH) has a lower proportion of polysaccharide chains that are at least 18 units long. Therefore, LMWH has a greater activity against FXa, whereas UFH has equivalent activity against both thrombin and FXa. Synthetic pentasaccharides only inhibit FXa.[22-25]

(c) patients with a thrombophilia such as PC or PS deficiency,[37] FV Leiden gene mutation, or lupus anticoagulant.[5,38-41]

Warfarin-Induced Purple Toe Syndrome

Warfarin-induced purple toe syndrome (WIPTS) is a rare but serious complication of warfarin therapy of which the dermatologist should be aware. WIPTS can develop within 2 to 16 weeks after warfarin initiation, but there have been reports of a delayed onset of over a year after commencing warfarin therapy.[11,12,42-44] WIPTS is often characterised by a sudden onset of a purple discoloration of the toes and sides of the feet that blanch with pressure. For the most part, the skin is intact, nonulcerated, and cool on palpation. This usually presents bilaterally but can occur unilaterally. Associated symptoms can include a burning pain and intermittent numbness.[11,12,42-44] In addition to the toes, this phenomenon has also been observed in the fingertips and palms.[11,12]

The mechanism contributing to WIPTS is still speculative. Earlier case reports suggested warfarin had direct toxic effect on the capillaries, whereas more recent reports suggest it is due to cholesterol crystal embolization.[42-44] The current theory is that warfarin causes the embolization of cholesterol crystals from atherosclerotic plaques in the large arteries, which dislodge into the small vessels of the toes and fingers. The embolus causes vessel occlusion and ischemia.[42,45,46] The evidence for this is supported by skin biopsies of the affected region, which show the presence of cholesterol emboli occluding the dermal arteries, resulting in ischemia of the epidermis.[42] The risk factors of WIPTS include (a) male sex, (b) advanced age, and (c) patients with atherosclerosis on long-term anticoagulation.[44,45]

Treatment involves warfarin cessation, and improvement can often be seen within 1 to 7 weeks.[44] Patients with WIPTS who require long-term anticoagulation should be switched to FXa inhibitors such as fondaparinux or apixaban.[44,47]

Warfarin-Hypersensitivity Reaction

Both urticaria and hypersensitivity reactions have been reported in patients taking warfarin. Transient urticaria has been reported within 40 minutes following warfarin initiation.[48] In contrast, the onset of a hypersensitivity reaction is variable and can occur within hours, days, or weeks following warfarin initiation.[49-51] Warfarin-induced hypersensitivity reaction often presents as a diffuse pruritic, morbilliform eruption that can occur anywhere on the body. Superficial erosions of the buccal mucosa have also been reported.[49-51] Skin biopsies of the affected areas show perivascular inflammation.[50] In all reported cases, the adverse reactions resolved once the warfarin was discontinued and reemerged with subsequent challenge. Warfarin-hypersensitivity reactions were reported to be ameliorated with prednisone/prednisolone, diphenhydramine, or histamine-receptor antagonists.[49-51]

Whether a personal or family history of an allergic diathesis predisposes patients to a warfarin-hypersensitivity reaction has not been established.[49-51] It has been suggested that warfarin likely induces both a type I immunoglobulin (Ig) E and type IV delayed T-cell hypersensitivity, although this has not been formally investigated.[51]

Heparins

Heparins are parenteral anticoagulants, and the term describes a heterogeneous population that includes unfractionated heparin (UFH), low molecular weight heparin (LMWH), and pentasaccharides. Heparins are highly sulphated polysaccharides belonging to the glycosaminoglycan family and are widely used anticoagulants.[22,52] UFH is isolated from animal tissue. Chemical or enzymatic depolymerisation of UFH results in the formation LMWH, which is ~30% of the size of the native molecule.[22,52] LMWH has better pharmacokinetic characteristics and fewer undesirable side effects than UFH, since there are fewer protein interactions and off-target effects.[23] Pentasaccharides are synthetic compounds that were developed to selectively inhibit FXa.[53] The different sizes result in 2 different molecules with different specificities and pharmacokinetics (Table 1 and Figure 2).

Table 2. Summary of the Adverse Drug Reactions Associated With Anticoagulation.

Adverse Drug Reaction	Signs and Symptoms	Management	References
Warfarin			
Warfarin-induced skin necrosis	• Petechiae and haemorrhagic bullae (<24 hours) • Necrotic skin, ulcers in subcutaneous fat (>24 hours) • Pain, paresthesia ± sensation of pressure	• Warfarin cessation, switch to DOACs • Skin debridement • Skin grafting if extensive • Early detection to avoid amputation	4, 5, 34, 35
Warfarin-induced purple toe syndrome	• Purple discoloration of phalanges, plantar surface, and medial and lateral aspects of the feet • Blanch with pressure and mostly bilateral • Burning quality pain and intermittent numbness	• Warfarin cessation, switch to DOACs or pentasaccharides	11, 12, 42-47
Immediate and delayed hypersensitivity	• Dermatitis presenting with diffuse pruritic, morbilliform eruption on body • Transient urticaria • Superficial buccal mucosa erosions	• Warfarin cessation, switch anticoagulation • Prednisone/prednisolone • Diphenhydramine • Histamine-receptor antagonists	49-51
Heparin			
Heparin-induced skin necrosis	• Pruritic, well-circumscribed, erythematous infiltrative plaques at injection site • Progression to skin necrosis • Systemic complications include thrombocytopenia and thromboembolism	• Heparin cessation, switch to warfarin or DOACs • Skin debridement • Skin grafting if extensive • Early detection to avoid amputation • Test sensitivities to a panel of heparins	4, 5, 54, 60, 62, 63
Immediate and delayed hypersensitivity	**Immediate hypersensitivity** • Urticaria, palmoplantar pruritus, angioedema **Delayed hypersensitivity** (more prevalent) • Pruritic and painful eczematous plaques at injection site • Progression to vesicles or bullae • UFH: risk of intertriginous and flexural exanthema (baboon syndrome)	• Heparin cessation, switch to warfarin or DOACs • Epinephrine, IV fluids ± vasopressors (as needed) • Antihistamines • Mix corticosteroids with heparin in same syringe or application of topical corticosteroids to injection sites • Test sensitivity to a panel of heparins	4, 14, 55, 57-60
Dabigatran			
Exanthematous drug eruptions	• Isolated or diffuse, pruritic, morbilliform exanthemas	• Dabigatran cessation, switch to warfarin	66-68
Leukocytoclastic vasculitis	• Diffuse, palpable purpura on trunk and limbs	• Dabigatran cessation, switch to warfarin • Methylprednisolone, dimethindene maleate, and H2 antagonists	69-70
Toxic epidermal necrolysis	• Diffuse erythematous macules on face and body • Progression to vesicles and flaccid bullae	• Dabigatran cessation, switch to different anticoagulant	71

Table 2. (continued)

Adverse Drug Reaction	Signs and Symptoms	Management	References
Rivaroxaban			
Exanthematous drug eruptions	• Erythematous and pruritic eruption • Neutrophilia and eosinophilia without infection	• Rivaroxaban cessation, switch to LMWH • Topical mometasone • Oral antihistamines • Liquid paraffin 50%/white soft paraffin	72
Urticaria and angioedema	• Diffuse urticaria, erythema, puritic lesions across body • Angioedema of eyes and lips, shortness of breath and bronchospasm	• Rivaroxaban cessation, switch to LMWH • Supplemental oxygen • Methylprednisolone IV • Antihistamine IV	73
Drug reaction with eosinophilia and systemic symptoms (DRESS)	• Pink, morbilliform rash on trunk and arms extending to axillae • Painful tenosynovitis of joints • Leukocytosis and eosinophilia • Biochemical tests suggestive of hepatic and renal injury	• Rivaroxaban, cessation switch to warfarin • Methylprednisolone	74, 75
Edoxaban			
Bleeding	• Subcutaneous haemorrhage, wound haemorrhage, postprocedural haematoma, wound haematoma	• Edoxaban cessation	76
Rash	• Not described	• Edoxaban cessation	76

DOACs, direct oral anticoagulants; IV, intravenous; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

Heparin-Induced Hypersensitivity Reactions

Hypersensitivity reactions are the most common cause of heparin-induced eruptions. Heparin-induced urticarial eruptions caused by both type I immediate and type IV delayed hypersensitivity reactions have been reported.[5,54] Of these, delayed hypersensitivity reactions are more commonly observed, with an estimated incidence of 7.5% in patients on subcutaneous heparin therapy.[3,55,56] Cutaneous lesions can initially manifest as pruritic and painful eczematous plaques that sometimes progress to vesicles or bullae at injection sites.[3,55,57-59] The depth of the heparin injections can also lead to different manifestations. Deep subcutaneous injections often lead to erythema and swelling, whereas more superficial administrations trigger a dermal and epidermal response, leading to the formation of vesicles or bullae.[54] Delayed hypersensitivity occurs after a heparin sensitisation period of at least 7 to 10 days but is commonly observed after weeks or months following heparin exposure.[60] Delayed hypersensitivity occurs most commonly with LMWH, followed by UFH, and is rarely seen with pentasaccharides.[3,56] However, UFH can induce a systemic sensitisation reaction characterised by fever, a generalised exanthem, or a systemic drug-related intertriginous and flexural exanthem (aka "baboon syndrome"). To date, life-threatening mucocutaneous reactions such as Stevens-Johnson or toxic epidermal necrolysis (TEN) have not been reported to be associated with any type of heparin.[54]

Immediate hypersensitivity reactions have several different manifestations that include urticaria, palmoplantar pruritus, dyspnea, angioedema, and anaphylaxis.[14,60] Immediate sensitisation to heparin has been reported with both UFH and LMWH.[14,55] These reactions are often due to the preservatives or contaminants in the heparin preparations derived from animal sources; this is now rarely observed due to the availability of preservative-free formulations.[14,60]

The mechanism of heparin sensitisation is similar to other drug reactions. Whereas immediate hypersensitivity reactions likely involve IgE, delayed-type reactions are cell mediated.[59,60] When biopsied, patients with a delayed-type heparin sensitivity exhibit histological changes that are consistent with 1 of 2 main patterns: (a) allergic dermatitis associated with spongiosis of the epidermis and vessel dilation with lymphocyte, histiocyte, and/or eosinophil infiltration or (b) drug reaction associated with lymphocytes and histiocytes invading the perivascular regions and eosinophils in the superficial dermis.[59]

Heparin-Induced Skin Necrosis

The cutaneous manifestations of heparin-induced skin necrosis (HISN) are clinically similar to WISN.[60] These cutaneous

Figure 3. Leukocytoclastic vasculitis. Nonblanching, palpable purpura observed on the anterior chest and abdomen of a patient with a drug reaction to dabigatran. This image was taken from Potolidis et al[70] and reproduced with the authors' permission from an open access article distributed under the Creative Commons Attribution License.

lesions typically present as pruritic, well-circumscribed, erythematous infiltrative plaques at sites of subcutaneous injection. However, if left untreated, they can rapidly become haemorrhagic and necrotic, affecting deep tissues and leading to limb gangrene.[54,61] Less commonly, skin necrosis can occur in areas that are distal to the subcutaneous injection site due to systemic involvement, and in such cases, associated complications often include thrombocytopenia and thromboembolism.[62,63] HISN is commonly observed within 5 to 10 days after initiation of heparin therapy, but a later onset of up to 16 days has also been reported. The prevalence of skin necrosis induced by UFH is greater than LMWH and is rarely observed in those on pentasaccharide therapy.[4,5,60]

Although the exact etiology is unclear, most patients with HISN concomitantly have heparin-induced thrombocytopenia (HIT type II, hereafter referred to as HIT) and thrombosis.[4,5,60] In HIT, the interaction between heparin and platelet factor 4 (PF4) (a platelet-specific chemokine) triggers an immune reaction leading to the formation of IgG antibodies to heparin-PF4. The ternary complex consisting of the drug-protein-antibody (heparin-PF4-IgG) is prothrombotic because it activates platelets, promotes thrombin generation, and causes endothelial injury.[60,64] Platelet levels decrease in HIT due to consumption and therefore can be used as a diagnostic tool. The antigen-antibody complex can also trigger a type III reaction, which is characterised by an inflammatory process leading to vasculitis.[55] Histology from patients seems to confirm the role of thrombosis and type III reactions in HISN. Fibrin-rich clots and leukocytoclastic vasculitis are present in the superficial dermal vessels with evidence of necrosis of the epidermis and dermis.[54,62,63]

Risk Factors and Management

Risk factors contributing to the development of cutaneous drug reactions to heparins include (a) female sex, (b) advanced age, (c) pregnancy, and (d) repeated exposures to heparins.[54,55] Having a comorbid condition such as hypertension, diabetes mellitus, obesity, connective tissue disease, or malignancy may also increase the likelihood of developing drug reactions to heparin.[4,5] Unlike warfarin, there seems to be no correlation between having thrombophilia and developing HISN.[4,5]

In patients with heparin sensitivities, subcutaneous testing of a panel of heparins and heparin-like molecules is recommended, since having one heparin reaction can predispose patients to other heparin sensitivities.[4,57,58] In particular, longer chained heparins have a greater tendency to illicit a delayed-type immune response than pentasaccharides.[65] In patients with heparin sensitivities requiring continual anticoagulation, it is recommended that patients start on pentasaccharides, nonheparins such as warfarin, the thrombin inhibitor hirudin, or DOACs.[4,5,54,57]

Drug Reactions to Dabigatran

Exanthematous Drug Eruptions

Morbilliform exanthemas are the most commonly reported drug reactions to dabigatran. A pruritic morbilliform eruption can present in an isolated region or diffusely on the body.[66-68] The time course associated with the eruption varies from 1 day up to 2 weeks after commencing dabigatran. In most studies, the symptoms were managed with prednisone and/or diphenhydramine. The eruption resolved within 5 to 7 days after dabigatran was discontinued and patients were switched to warfarin. It is important to note that in most cases, the patients were not rechallenged, nor was skin testing conducted to confirm the drug reaction. The Naranjo score, however, suggested a probable reaction to dabigatran.[66-68]

Leukocytoclastic Vasculitis

To date, there have been 2 reported cases of leukocytoclastic vasculitis due to dabigatran. In both instances, the patients were over 70 years old, and both exhibited palpable purpura distributed diffusely along the trunk and limbs after 1 week of being on dabigatran (Figure 3).[69,70] One patient also experienced pruritus and a burning sensation associated with the lesions.[58] Skin biopsies revealed endothelial swelling and neutrophil infiltration of the vessels associated with tissue damage and necrosis, consistent with cutaneous small vessel vasculitis.[69,70] Despite having a similar presentation, 1 patient's symptoms were resolved within 72 hours of oral prednisolone treatment. In contrast, the other patient was nonresponsive to a combination of methylprednisolone, dimethindene maleate, and H2

antagonists.[57] In both cases, the lesions were ameliorated once dabigatran was discontinued and patients were switched to warfarin or LMWH.[69,70]

TEN

There was 1 reported case of TEN in a patient taking dabigatran for 5 weeks and on an iron supplement for 9 days.[71] The patient had erythematous macules widely distributed on the face and body that lasted 5 days. Associated symptoms included pain and a burning sensation of the affected areas of the skin. The cutaneous lesions later manifested into vesicles and flaccid bullae that culminated in extensive sloughing of the skin. The Nikolsky sign was positive, and the eruption involved 72% of the patient's body. The patient also had conjunctivitis. Preceding the rash, the patient had flu-like symptoms, which was consistent with an acute and severe bullous disorder due to a drug reaction. Since the patient was taking both an iron supplement (succinylate) and dabigatran, it was difficult to determine whether the drug reaction was due to the anticoagulant, the iron supplement, or a drug-drug interaction involving both agents.[71]

Drug Reactions to Rivaroxaban, Apixaban, and Edoxaban

Overall, the reported incidence of dermatologic immune reactions and anaphylaxis or anaphylactic shock associated with FXa inhibitors is <0.1%.[3] Several cutaneous drug reactions have been reported with rivaroxaban and few with edoxaban, but to date, there have been no reports of eruptions associated with apixaban.

Drug Reactions to Rivaroxaban

Exanthematous Drug Eruptions

One patient taking rivaroxaban was reported to have developed acute generalised exanthematous pustulosis.[72] An erythematous and pruritic eruption in the groin region was noted within 48 hours of commencing rivaroxaban. Within a week, the eruption had spread over the body and face. Complete blood count revealed an elevated white blood cell count, with neutrophilia and eosinophilia in the absence of infection. Rivaroxaban was discontinued, and the patient was switched to LMWH. The eruption resolved with oral antihistamines, topical mometasone, and liquid paraffin 50%/white soft paraffin.[72]

Urticaria and Angioedema

Rivaroxaban was reported to cause generalised urticaria, erythema, severe pruritus, and angioedema of the orbital area and lips.[73] The patient also experienced shortness of breath and bronchospasm likely due to angioedema of the

respiratory tract. Rivaroxaban was discontinued and the patient was managed with supportive oxygen, intravenous antihistamines, and methylprednisolone (60 mg).[73]

Drug Reaction With Eosinophilia and Systemic Symptoms

There is 1 report of an elderly patient with a severe drug reaction with eosinophilia and systemic symptoms (DRESS) and organ injury after 6 weeks of rivaroxaban.[74] The patient presented with a pink morbilliform eruption on the trunk and inner side of both arms that extended to the axillae. Associated symptoms included fatigue, painful tenosynovitis of several joints, and pitting edema. Laboratory tests were suggestive of hepatic and renal injury, with associated leukocytosis and eosinophilia, without evidence of infection. Histopathology showed perivascular infiltration of lymphocytes, eosinophils, and neutrophils consistent with a dermal hypersensitivity reaction. Rivaroxaban was discontinued, and the patient was switched to warfarin. Additional management included methylprednisolone, and within a week, there was marked improvement.[74] Although this was the first report of DRESS associated with rivaroxaban, this was the third case of drug-induced hepatic injury in patients on rivaroxaban.[74,75]

Drug Reactions to Edoxaban

Subcutaneous Haemorrhage, Wound Haemorrhage, and Rash

To date, there have been very few reported cases of cutaneous reactions with edoxaban. An early postmarketing study of edoxaban in Japan showed that 0.3% (56/20 000) of patients reported 1 or more adverse reactions with edoxaban.[76] In total, 67 adverse drug reactions were reported, and the majority of these were related to bleeding complications. Subcutaneous haemorrhage was reported in 18% (12/67) of the cases, with 4% (3/67) of these bleeding events being classified as serious bleeding. Other relevant bleeding complications included wound haemorrhage, postprocedural haematoma, and wound haematoma, with a few of these cases reported as serious. This may be relevant to dermatologists performing procedures in their office, highlighting the need to be aware of these newer agents when taking a medication history. Nonspecific rash was the other cutaneous reaction observed with edoxaban, but this accounted for less than 2% (1/67) of the reported adverse reactions.[76]

Summary

Anticoagulants are widely used drugs that can lead to potentially debilitating and life-threatening adverse drug reactions. When assessing a patient with a potential drug

eruption, it is important for the dermatologist to be aware of the newer DOAC agents as well as traditional anticoagulants. Early recognition of the cutaneous signs and symptoms and timely management can prevent morbidity and mortality. Most reports to date are hypersensitivity reactions to an anticoagulant.[3] In more concerning cases, patients developed skin necrosis and/or systemic complications. Warfarin and heparin have been used for decades, whereas DOACs have only been available for the past few years. DOACs have the advantage of being oral drugs that have improved pharmacokinetics and do not require regular monitoring. As more patients switch to DOACs, dermatologists should be aware of the potential associated cutaneous manifestations. In the event of an adverse drug reaction, the offending agent should be discontinued and, through communication with the prescribing physician, the anticoagulant switched to a safer alternative.

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