General

Anticoagulant-related skin reactions

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Cutaneous reactions have been reported during anticoagulant therapy with coumarin derivatives, unfractionated and low molecular weight heparins, heparinoids, danaparoid and hirudins. Anticoagulant-induced skin reactions vary from local allergic manifestations to skin necrosis. In patients with allergic reactions, diagnosis and crossreactions between anticoagulants can be confirmed by intracutaneous testing. Coumarin- and heparin-induced skin necrosis are rare, but are important side effects due to their high morbidity and occasional mortality. Cutaneous tests are contraindicated in these patients. In the future, anticoagulant strategies may include direct synthetic thrombin inhibitors (argatroban and melagatran/ximelagatran) and the Factor Xa inhibitor, pentasaccharide (fondaparinux).

Keywords: coumarin, fondaparinux, heparin, hirudin, skin reactions, ximelagatran


1. Introduction

It is believed that the first description of an anticoagulant-induced skin necrosis was in 1943, however, the breast necrosis in the 49-year-old woman was, at the time, attributed to thrombophlebitis migrans disseminate [1]. From the 1950s onwards, skin necrosis has been associated with oral anticoagulation [2] and, until June 2002, approximately 400 cases have been reported worldwide, according to Medline-based research. Heparin-induced skin lesions have been published, although less have been published for low molecular weight heparin (LMW-heparin), with approximately 100 cases in total [3].

Skin lesions induced by anticoagulants can appear as allergic or necrotic reactions. Local allergic skin reactions often show painful red plaques appearing 2 – 3 days after starting anticoagulant therapy. Immunological reactions start after 7 or more days [3]. Heparin-induced skin necrosis can occur at the injection site as well as at any other site of the skin after subcutaneous or intravenous administration, and has been frequently reported in association with heparin-induced thrombocytopenia (HIT) [3-5].

2. Coumarin-induced skin necrosis

Coumarin-induced skin necrosis is a rare complication of oral anticoagulation with a prevalence reported to be between 0.01 and 0.1% of patients [6].

2.1 Aetiology
The exact aetiology of coumarin-induced skin necrosis is still unknown, but is often associated with a hypercoagulable state. Protein C or protein S deficiencies have been reported in patients with coumarin-induced skin necrosis as well as in those with Factor V Leiden, mutation of the prothrombin gene, lupus anticoagulants and antiphospholipid syndrome [7-9].
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Protein C deficiency is widely accepted as a major risk factor for coumarin-induced skin necrosis. Rose et al. examined protein C level antigens in blood samples of 13 patients with a previous warfarin-induced skin necrosis and in 11 patients, a low protein C level was found, showing the implication of low antigen levels of protein C in the pathogenesis of warfarin necrosis.

After introducing coumarin therapy, vitamin K-dependent protein C and Factor VII levels drop rapidly, compared with other factors such as Factor IX and X and prothrombin, leading to a procoagulant/anticoagulant imbalance. The depression of protein C, together with a low blood velocity, leads to necrosis, particularly in the microvascular system. A similar mechanism may induce local necrosis in protein S deficiency, resistance against activated protein C (APC resistance) and lupus anticoagulants.

The transient hypercoagulability leads to local thrombotic occlusions in the small vessels followed by necrosis. During steady-state of the vitamin K antagonists, hypercoagulability occlusions in the small vessels followed by necrosis. During steady-state of the vitamin K antagonists, hypercoagulability leads to haemorrhage in the necrotic area.

Microscopic pictures of the necrotic areas show pathological changes in microcirculation-rich areas with thrombosis, microvascular injury and fibrin deposits in the postcapillary veins and small vessels, haemorrhage and diffuse necrosis in the dermis and subcutaneous adipose tissue.

2.2 Symptoms

Most patients (i.e., more than two thirds) are obese, middle-aged women, often treated with coumarin derivatives for a thromboembolic disease. Predilection sites of the lesions are areas with increased subcutaneous fatty tissue, e.g., breast, thigh, abdomen and buttock (Figure 1).

Symptoms start within 10 days after the onset of therapy with pain, oedema and small subcutaneous haematomata, followed by erythematous or haemorrhagic changes in demarcated lesions, that become bullous and can progress to gangrenous necrosis [11,12]. Symptoms are often associated with a large initial loading dose of coumarin derivatives. Delayed onsets have also been reported between day 15 up to 2 years after introducing coumarin therapy.

Reports of coumarin-induced skin necrosis are mainly attributed to warfarin but are also seen with other coumarin derivatives.

2.3 Treatment

As soon as skin reactions appear in a patient treated with coumarin derivatives, the oral anticoagulant has to be discontinued. Anticoagulant therapy should be continued with heparin or LMW-heparins until the necrotic lesion heals. Even though heparin itself can cause a skin necrosis, there are no reports in the literature that heparin-induced skin necrosis followed a coumarin-induced skin necrosis or vice versa.

Small lesions may be treated conservatively, but progression of the necrotic changes may require surgical intervention. Regression of skin necrosis has been described using a protein C concentrate in patients with protein C deficiency [14]. Successful reintroductions of oral anticoagulation have been reported [6,15]. To minimise the risk of recurrent skin necrosis, oral anticoagulation therapy with warfarin was started at 1 mg/day with a very slow increase in the dose.

2.4 Other coumarin-induced cutaneous reactions

Allergic dermatitis is another complication of coumarin therapy with various clinical manifestations. It appears as urticaria, maculopapular erythematous rash or vesicular rash between 2–3 days or up to months after treatment. The skin reactions usually disappear when coumarin therapy is discontinued, especially in the case of allergic dermatitis where differential diagnosis of the sensitising agent may be important.

Another unusual complication can be a hypersensitivity reaction such as vasculitis, which in severe cases can mimic a skin necrosis. In contrast to coumarin-induced skin necrosis, vasculitis may appear at any time and is accompanied by pathological laboratory values and an inflammatory infiltrate at histological examination. Another adverse reaction is the purple toe syndrome, which was described in 1976 as an acute digital cyanosis secondary to microembolism from a proximal atheromatous source. An association with anticoagulant therapy was already established in 1981 and the symptoms were attributed to cholesterol emboli released as a result of coumarin-induced bleeding into atheromatous plaques. Characteristic findings include the sudden development of blue or purple areas on the sides of feet and toes which are painful and tender to touch, and usually occur 3–8 weeks after introducing coumarin therapy. The lesions are often bilateral and persist for several weeks.

2.5 Prophylactic measures

Anticoagulation should be started with heparin or LMW-heparin, while oral anticoagulation with coumarin derivatives should be introduced with small or moderate doses. Loading doses should be avoided. Heparin/LMW-heparin therapy should be maintained until INR > 2 (international normalised ration of the prothrombin time) are obtained twice on two consecutive days.

3. Heparin-induced skin reactions

Allergic skin reactions or skin necrosis to heparin and LMW-heparin are rare but the incidence is probably underestimated due to under-reporting.

3.1 Aetiology and pathogenesis

The aetiology of heparin-induced skin necrosis is unknown but the occurrence is often associated with HIT (HIT Type II). HIT Type II is an immunological reaction leading to the binding of heparin to platelet factor-4 (PF-4), which induces the production of heparin-dependent IgG, IgM and IgA antibodies.
Elevated IgG antibody titres were also observed in patients with heparin-induced skin lesions irrespective of whether they developed thrombocytopenia, suggesting an immunological mechanism in these patients [3]. A high association between heparin-induced cutaneous lesions with positive testing for LMW-heparin and danaparoid, circulating antiheparin IgG antibodies and HIT Type II has been described [4].

3.2 Clinical picture

There is a broad spectrum of cutaneous reactions from erythematous pruritic areas to large symptomatic plaques (Figure 2) to heparin-induced skin necrosis (Figure 3). Women are more affected than men [23].

Heparin-induced skin necrosis starts between day 5 and 10 after introduction of intravenous or subcutaneous administration. Late onsets, i.e., up to day 16, have been reported [24]. Skin necrosis occurs more often in patients treated with unfractionated heparin than with LMW-heparin [25,26]. The necrosis starts with a small, erythematous and painful lesion that later extends to areas of necrosis [24]. Histological findings show microvascular thrombi in small vessels with minimal inflammation [27].

When skin reactions appear, intracutaneous testing should be performed to confirm diagnosis and to rule out cross-reactions between different LMW-heparins and danaparoid. Importantly, cross-reactions between heparin and LMW-heparins are observed in 50 and 100% and with danaparoid in up to 65% of patients [4]. Koch et al. examined 23 patients with delayed hypersensitivity reactions after subcutaneous heparin injections and found 19 patients who were sensitised to all the heparins and LMW-heparins tested [28].

3.3 Treatment

When local cutaneous allergic reactions to heparin appear, therapy can be continued until the results of cutaneous testing are available. The therapy should then be changed according to the test results (Figure 4).

Discontinuation of medication is mandatory if systemic allergic reactions have occurred [3]. Switches from subcutaneous to intravenous administration of heparin have been described but this, in turn, can cause generalised reactions [29]. Anticoagulant therapy should be changed to Hirudin and/or coumarins and cutaneous testing should be performed. Depending on the results of the test, anticoagulant therapy may be continued or should be changed. In the future, argatroban, melagatran or fondaparinux may be adopted.

Heparin PF-4 antibodies should be determined and a thrombophilic screening performed. Prophylactic, low doses of the alternative anticoagulant are recommended for patients without thrombophilic tendency and who test negative for heparin PF-4 antibodies. Therapeutic high doses are recommended for patients who test positive for heparin PF-4 antibodies [3,4].

3.4 Other heparin-induced skin reactions

Skin lesions may appear at the injection site but can also be generalised. Immediate as well as delayed hypersensitivity reactions may occur [5]. Skin reactions have been reported as urticarial rash or as a Type I immediate hypersensitivity reaction and usually appear 2 – 5 days after the start of treatment. They can also occur as Type III Arthus reaction with vasculitis. Delayed hypersensitivity reactions may be present with localised skin reactions [30] or with a generalised maculopapular rash [31], within days 3 and 14 of therapy [30].

3.5 Differential diagnosis

Local allergic reactions to sprays or other ingredients of subcutaneous heparin formulations have also been described [32].

4. Hirudin-induced skin reactions

Hirudin is an enzyme produced by the salivary glands of the leech Hirudo medicinalis and acts as a specific direct
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Thrombin inhibitor. Today, recombinant DNA technology is used for production. Pegylated-hirudin was developed to increase the half-life of r-hirudin [33] and to reduce the antigenicity of hirudin.

4.1 Aetiology

The polypeptidic nature of hirudins can cause an immunogenic reaction in some individuals. IgG and IgE antibodies against r-hirudin develop in 40 – 70% of patients with hirudin-induced skin reactions. Immediate as well as delayed hypersensitivity reactions have also been reported.

4.2 Symptoms

Allergic reactions after hirudin exposure appear as urticaria after systemic administration [34] or as contact allergy following topical use [35].

Re-exposure to hirudins was investigated in healthy subjects. Out of 200 volunteers, only 3 experienced an allergic reaction after the second course of subcutaneous r-hirudins. Thus, the conclusion was that Type 1 allergic reactions to r-hirudin are rare (< 1%) after a second exposure and limited to the skin [36].

In a case report, an allergic reaction to r-hirudin was described in a patient with a history of HIT [37]. Twenty mins after subcutaneous injection of r-hirudin, the patient developed pruritus, erythema and a generalised flush reaction. After therapy with cortisone and histamine antagonists, the symptoms disappeared. Under treatment with pegylated-hirudin 50 mg s.c. o.d., no side effects occurred.

Another report in the literature described a patient with a history of HIT Type II. During bolus injection of hirudin, extravasation in the surrounding tissue occurred. Infusion was restarted at a different site for 10 days. After 4 weeks, the patient developed skin reactions with erythema and induration at the site of extravasation. Histopathological findings showed an epitheloid granulomatous infiltrate. The findings and delayed onset were consistent with a delayed hypersensitivity reaction to hirudin [38].

Jappe et al. reported the occurrence of a local Arthus reaction after subcutaneous application of r-hirudin in a female patient with delayed-type hypersensitivity to several heparins and heparinoids. The patient was then challenged with intravenous heparins and heparinoids for 5 days and tolerated this treatment well [39].

4.3 Treatment

If skin reactions to r-hirudin appear, treatment may be continued with argatroban, melagatran or pentasaccharide. Subcutaneous or intravenous administration of heparin/LMW-heparin, danaparoid or dermatansulfate may also be an alternative if the patient had no adverse events or positive cutaneous testing.

5. Decision rules and perspectives

Skin reactions are rare adverse effects of anticoagulant therapy and can occur with treatment with coumarin-derivatives, heparins, LMW-heparins, danaparoid and hirudins. Coumarin- and hirudin-induced skin necrosis are serious complications and are associated with a high morbidity and occasional mortality [40,41]. Patients with coumarin-induced skin reactions can continue anticoagulant therapy safely and effectively by switching to heparin treatment. Rules for deciding an alternative therapy when cutaneous allergic and necrotic reactions occur are summarised in Figures 5 and 6.

In cases of heparin-induced skin reactions, intracutaneous testing should be performed before switching to another LMW-heparin or danaparoid sodium to rule out...
Figure 5. Decision rules for treatment of anticoagulant-induced allergic reactions.
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Figure 6. Decision rules for treatment of anticoagulant-induced skin necrosis.
crossreactions. If positive cutaneous testing is found for all tested agents, anticoagulant therapy with hirudin should be offered as an alternative (Figures 5 and 6). In the future, pentasaccharides or oral thrombin inhibitors may be the alternatives.

6. Conclusions

The aim of this article was to briefly review the most relevant issues of anticoagulant-related skin reactions and the management for diagnosis and further anticoagulation. A local manifestation of allergic skin reactions should not immediately lead to therapeutic changes of anticoagulant therapy. In these patients, cutaneous testing is advisable due to crossreactions between coumarins and heparins/LMW-heparins/danaparoid.

If systemic allergic reactions occur, then alternative anticoagulant therapies should be used although cutaneous testing is still advised. In contrast, if coumarin- and heparin-induced skin necrosis should occur, then there should be an immediate termination of the anticoagulant, and treatment should be changed to therapeutic doses of an alternative anticoagulant (Figure 6). Cutaneous testing is contraindicated in these patients.

7. Expert opinion

The authors wish to end this review by proposing the following principles:

• Anticoagulant-related skin reactions are rare and should not lead to any screening of coagulopathies in patients with indications for anticoagulant therapy before starting the treatment.

• Cutaneous allergic reactions to coumarins or heparins/LMW-heparins/danaparoid should be clearly identified by excluding other causes.

• Cutaneous testing is indicated in patients with cutaneous allergic reactions to anticoagulants because they lead to the therapeutic consequences. The test results should be documented in an allergy passport.

• Anticoagulant skin necrosis is severe and may be life threatening. Development of new anticoagulants offers the possibility of treating these patients effectively due to the high thrombophilic diathesis in such situations.

• Cutaneous testing is contraindicated in patients with anticoagulant-induced skin necrosis.

• The development of cutaneous allergic reactions may also occur with the newer anticoagulants, including those of a synthetic origin. New synthetic Factor Xa or thrombin inhibitors are very unlikely to become antigenic.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (**) to readers.


9. Description of the pathomechanism of coumarin-induced skin necrosis via the protein C/protein S pathway of blood coagulation.


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** Relevant documentation that with the mean steady-state dose of 5 mg warfarin, the therapeutic INR is obtained as fast as with a loading dose of 10 mg warfarin. This reduces the possibility of developing a transient protein C deficiency responsible for the coumarin-induced skin necrosis.


** Description of an anticoagulant strategy in a patients with multiple allergies to heparins, heparinoids and hirudin.


** American-Canadian guidelines for antithrombotic therapy.


