

Probable cutaneous allergic response to subcutaneous heparin - a case report

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S U M M A R Y

Heparin is a heterogeneous mixture of sulfated mucopolysaccharides, commonly used injectable anti-coagulant. It is known to cause cutaneous adverse reactions like eczema, erythematous plaques, exfoliative dermatitis and tissue necrosis. We report a case of probable cutaneous allergic response caused by injection of heparin with an established causality and severity. The reaction developed after stopping the drug therapy and after the patient had already been discharged. Since heparin is a widely used drug and this reaction can manifest even after the drug therapy has ceased, thorough counseling of the patient is mandatory.

Introduction

Heparin is a heterogeneous mixture of sulfated mucopolysaccharides which binds to the endothelial cell surfaces, and acts on the plasma protease inhibitor, antithrombin III (AT III). For this reason it is used as an anti-coagulant (1). Heparin is known to cause cutaneous adverse reactions like eczema, erythematous plaques, exfoliative dermatitis and tissue necrosis (2). We hereby report a case of cutaneous allergic response caused by injection of heparin with an presumed causality and severity supported by the Naranjo algorithm (3) and the Hartwig scale (4).

Case report

A 36-year-old female was admitted to the surgery ward of Manipal Teaching Hospital, Pokhara, Nepal with complaints of a painful swelling over the calf and the back of right side of the knee, the pain being aggravated on standing. Clinical examination at the surgical ward revealed swelling of right leg with tenderness over calf. Tortuous veins over calf and popliteal fossa were prominent. There was no ulceration or pigmentation of skin. The attending surgeon made a provisional diagnosis of deep vein thrombosis. Venous Doppler study of the lower limbs revealed thrombosis of left and right anterior and posterior tibial

K E Y W O R D S

**allergy,
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assessment**



Figure 1. Erythematous plaques with scaling over the left upper arm.

veins, thus confirming the diagnosis. The initial prothrombin time (PT) of the patient was 22.01 seconds (control 12.99 secs) and the INR was 2.2. The patient was started on an initial injection of heparin 10,000 units, followed by 5000 units subcutaneously three times a day, for a total period of 5 days. In the days between the admission to



Figure 2. Erythematous scaly plaque studded with tiny vesicles over the left thigh

the hospital and the appearance of the skin lesions the patient was receiving following tablets: warfarin 5 mg once daily, aspirin 75 mg once daily and ranitidine 150 mg twice daily.

Eleven days later (16 days after starting the drug therapy) the patient presented to the dermatology Outpatient department with complaints of an itching and burning sensation all over the injected sites. On examination, the patient had erythematous non-tender papules and plaques studded with tiny vesicles over the sites, where subcutaneous heparin injections have been applied on both arms (figure 1), on the thigh (figure 2), on the left wrist and forearm. A provisional clinical diagnosis of cutaneous allergic response to subcutaneous heparin was made. No systemic disorders such as bleeding disorders, thrombocytopenia, mastocytosis that could have predisposed the patient to such reaction, were noted. It is known that warfarin and aspirin may eventually trigger similar manifestations. In such case, the symptoms are usually generalized, and not only at the site of heparin injections. For this reason we attribute the adverse reaction to heparin injections.

The patient was put on oral prednisolone 40 mg daily, which was later tapered and stopped. She was also given tablets: chlorpheniramine 25 mg once in the night, cetirizine 10 mg once daily and Fluticasone dipropionate cream topically. The lesions subsided within 10 days.

We carried out the causality assessment by the Naranjo algorithm and found that the ADR to heparin was probable, the Naranjo score being 6 (3). The patient did not consent to the rechallenge, and she also refused the patch/intradermal tests. The severity assessment by the Hartwig scale (4) revealed the ADR to be of 'Moderate level 3'.

Discussion

There are several reports of allergic reactions attributed to subcutaneous heparin. In one study, fifteen patients (14 females) developed erythematous, infiltrated plaques 3 to 21 days after beginning SC heparin therapy. These plaques were considered to be delayed hypersensitivity reactions after subcutaneous, intracutaneous and epicutaneous testing with heparin (6).

Carrozza et al have reported a case with pruritic, erythematous plaques developing at the sites of injection of calcium heparin 72 hours after the first injection in an elderly lady. Heparin was confirmed as the causative agent by patch and intradermal testing. Substitution with a low molecular weight heparin produced a similar reaction (7).

Exfoliative dermatitis has been reported with intermittent heparin therapy in a 66 year old female hospitalized for sepsis and undergoing hemodialysis for acute renal failure. After the second hemodialysis session, she

developed a diffuse, desquamating, erythematous, maculopapular rash, which worsened after each session and was accompanied by rising eosinophil counts (8).

Skin necrosis has been reported in patients treated with unfractionated heparin and also reported occasionally in patients treated with low molecular weight heparin preparations (9). Erythematous nodules or infiltrated and sometimes eczema-like plaques at the site of injections are potential side effects of subcutaneous application of unfractionated heparin, probably due to delayed type hypersensitivity reaction. It can be observed even with low molecular weight heparin (10).

The exact mechanism provoking the dermatological reactions to heparin is poorly understood. Heparin can cause Type I to Type IV hypersensitivity reactions manifesting as skin reactions, heparin-induced thrombocytopenia (HIT) and anaphylaxis (11, 12). Low molecular weight heparins are also known to cause allergic eczema-like lesions (delayed type hypersensitivity reaction) and erythematous plaques or necrosis (Arthus type reaction) (13).

In the case of allergic cutaneous reaction to subcutaneous heparin, it has been emphasized that changing heparin administration to the intravenous route should be avoided as potentially unsafe (14).

Treatment options for patients allergic to a specific heparin preparation can be determined by skin tests with various heparin preparations, which may be helpful in detection of cross-reactivity between different low molecular weight heparins and unfractionated heparin.

Causality assessment using standard methods is probably the best way to establish the causal relationship between a drug and its effect. The Naranjo algo-

rithm (3) is used widely in assessment of ADRs. It is based on the score calculated on the basis of points assigned to each of ten questions that makes up the table. On a scale with maximum of 13 points the score greater than 9 confirms the adverse reaction by the incriminate drug. A score of 5-8 is considered as probable, while a score of 1-4 is categorized as a possible ADR. In our case, the causality assessment indicated that the ADR was probably caused by heparin injection.

Moreover, the concomitant drugs such as aspirin and warfarin could have predisposed the patient to the reaction. It is known that warfarin and aspirin may trigger similar skin manifestations (15), such cutaneous manifestations are, however usually generalized, and are well documented in the literature (16).

In order to take appropriate initiatives towards management of the ADR, it is necessary to assess the severity of the ADRs, and the Hartwig scale (3) is widely used for the purpose. This scale categorizes the ADRs into different levels as mild, moderate or severe, which is helpful in deciding whether hospitalization is required.

Conclusion

We are reporting this case to stress the fact that heparin can cause various allergic reactions, although skin necrosis is the major side effect reported so far. Heparin being a commonly used drug and allergic reactions including contact dermatitis are known complications, monitoring of the patient is required even after the patient is discharged.

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