Editorial

Heparin Allergy: Frequently Suspected, Seldom Proven, and Easily Circumvented

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Heparin allergy is frequently suspected or expressed as a diagnosis by patients and physicians. The incident in question is usually poorly documented or not documented at all, and the suspicion is rarely proven by accurate diagnostic testing. However, the problem might turn urgent if a patient reporting a vague history of heparin allergy needs acute anticoagulation for prophylaxis or treatment for some thromboembolic disorder.

Heparins may cause clinical conditions of allergy or resembling an allergy, due to a variety of pathomechanisms. These range from heparin-induced thrombocytopenia of type I or II, via immediate hypersensitivity reactions, to delayed allergic skin reactions. The resulting clinical manifestations are diverse, varying from local skin reactions to skin necrosis and toxic epidermal necrolysis, from urticaria to bronchospasm and anaphylactic shock.[1] In daily life, the vast spectrum of anticoagulants, including unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), synthetic heparinoids, and synthetic pentasaccharides (such as fondaparinux), tend to confuse clinicians, who then declare the presence of a heparin allergy. Besides, patients might report being allergic to several heparins they had tried since cross-reactivity among LMWHs is a common problem.[2]

In the majority of cases, the presumptive diagnosis of a heparin allergy is based on the observation of local reactions such as erythema, papules, and pruritus after the injection of LMWH. A generalized maculopapular rash is less common. Therefore, guesswork is commonly used to trace the cause of the reaction, and subsequent actions may be inappropriate. The authors of the current report[3] described the solution to this problem for the majority of patients 17 years ago:[4] 28 patients with a proven delayed-type hypersensitivity (DTH) to subcutaneous heparin were challenged with intravenous heparin, which was well tolerated by all of them. The evidence of tolerance was also adopted as a recommendation in a standard publication on drug allergy:[5] "Patients with cell-mediated delayed hypersensitivity to LMWH may tolerate UFH or the same product intravenously. In all life-threatening emergency situations, such patients could receive UFH intravenously." However, this solution remained largely unknown or was not given sufficient importance in daily clinical practice. The authors of the original study called for a prospective study as soon as their retrospective report was published.[4] They initiated, conducted, and have now completed the investigation, which yielded clear results.[3] Challenge testing of patients suffering from DTH, which is the most common manifestation of a heparin allergy causing an inflammatory skin reaction at the site of subcutaneous injection, demonstrated that all of them tolerated intravenous heparin infusion well. The vast majority of these patients also tolerated subcutaneously administered fondaparinux.

Compartment allergy, a term proposed for an allergic reaction that only manifests when the causative allergen is introduced in a certain compartment or anatomical site, appears to be a phenomenon with hitherto ambiguous mechanisms.[6] The tolerance may be due to the failure of a particular protein to form an allergen, different antigen-presenting cells, or a "compartment" effect because of T-cell homing.[5] A similar dependence of hypersensitivity on the depth of subcutaneous injection has been described for local anesthetics.[6]

The current study[3] implies that patients with a confirmed diagnosis of DTH to LMWH should be issued an allergy document[7] not only stating their allergy but, even more importantly, that heparin can be safely administered intravenously. However, an essential prerequisite is to prove the DTH mechanism by prick and intradermal skin testing.[8] If the patient wishes to continue the treatment with subcutaneous injections, the latter can usually be initiated with fondaparinux. Only 6.3% of patients with a DTH to LMWH show cross-reactivity with this substance. However, a potential cross-reactivity must be ruled out in advance by provocation testing.[2,3] In addition, the most relevant differential diagnosis of DTH to subcutaneous heparins, the rare heparin-induced skin necrosis, is a clinical manifestation of heparin-induced thrombocytopenia and should also be ruled out.[9] And in urgent cases, the switch from subcutaneous to intravenous heparin is possible and useful even without prior diagnostic investigations for allergy.[3]

Thus, we have a feasible solution to the problem of a suspected heparin allergy. However, the pathomechanism of the triggering incident must be clarified soon after the reaction by appropriate testing, and the test should be adequately documented. In fact, this requirement applies to all adverse incidents resulting from the administration of a drug.[10]

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