"Heparin Allergy" Secondary to Preservative, Namely Benzyl Alcohol

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Abstract: Heparin is an injectable anticoagulant that prevents coagulation. There are presently high and low molecular heparins as well as synthetic pentasaccharide inhibitors. Given its ubiquitous use in sensitive medical states, there is a high concern for safety with this drug.

Heparin can induce several distinct immune-mediated reactions. There are several options to consider when heparin allergy occurs including use of direct thrombin inhibitors such as lepirudin and bivalirudin.

Of significant relevance, one must make sure that what appears to be heparin allergy is not, in reality, a reaction to a preservative. Benzyl alcohol is used as a solvent and preservative in many products including high and low molecular weight heparin and heparin lock flush solution. Allergic contact dermatitis from benzyl alcohol is well known and is on many lists of recommended patch test lists for preservatives.

Heparin is a highly-sulfated glycosaminoglycan that is an injectable anticoagulant that prevents clot formation. Thus, the agent is used in patients for thrombotic disorders or in situation in which blood clots are otherwise eminent. Such instances include deep vein thrombosis, pulmonary emboli, myocardial infarctions, and strokes.

Heparin is a biological substance that works by activating antithrombin III and thereby blocking thrombin from clotting blood. Heparin can be used by injection, or can be used on medical devices to prevent similar clot formation.

There are now more highly processed products available referred to as low molecular weight heparin. They also are administered subcutaneously, but given their predictable clinical results, do not require strict monitoring. Examples include enoxaparin (Lovenox and Clexane), certoparin (Sandoparin), ardeparin (Normiflo), parnaparin (Fluxum), tinzaparin (Innohep and Logiparin), dalteparin (Fragmin), reviparin (Clivarin), and nadroparin (Fraxiparin). These agents have fewer side effects and have more predictable plasma levels.

Additionally, there are synthetic pentasaccharide inhibitors of factor Xa. Fondaparinux (Arixtra) and Idraparinux are examples of these synthetic five sugars in heparin that form the high affinity biding site to antithrombin III. These agents are also administered subcutaneously.

Heparin-induced IgE-mediated hypersensitivity and anaphylactoid reactions are rare but well-described entities [1-3]. Three distinct immune-mediated reactions have been described [1]. First, there is an immediate type I hypersensitivity reaction with urticaria, angioedema, and/or bronchospasm. Secondly, there is a heparin-induced thrombocytopenia caused by IgG antibodies inducing platelet activation. This is a progressive type III hypersensitivity that occurs within ten days of initiating therapy. Lastly, a delayed type IV hypersensitivity has been described in which erythematous plaques and eczematous patches occur within either hours or after twenty days of treatment [4].

When heparin allergy occurs, there are several options. The first option is a tad risky, but due to the transient nature of antibodies causing heparin-induced thrombocytopenia, one can often restart heparin after a short delay [1, 5, 6]. Secondly, heparin has been combined with potent short-acting platelet agents to attenuate the immununologic reaction [6]. Alternatively, substitution to one of the low molecular weight heparins and/or synthetic pentasaccharide inhibitors has been successful [1, 2, 7]. However, delayed-type hypersensitivity to high and low molecular weight heparins does occur [4]. Another option is using a non-heparin agent, namely, direct thrombin inhibitors such as lepirudin and bivalirudin [6]. These agents specifically bind to the catalytic site and the anion-binding exosite of circulating and clot-bound thrombin. They are clearly different in chemical structure to heparin preventing any cross-reactivity [1, 4].

However, of paramount importance, is to realize that what appears to be heparin allergy, may actually be a reaction to its preservative, such as benzyl alcohol. For example in the Fig. (**1**), a 32-year-old female with a history of injection site reaction to high molecular weight heparin previously, developed several localized pruritic eczematous and hemorrhagic lesions on her abdomen within a day of injection of a low molecular weight heparin, namely enoxaparin. Later it was determined that she was reacting to benzyl alcohol, and not the heparin at all.

Benzyl alcohol (BA) is commonly present in natural products such as flavors, essential oils, balsam of Peru, and balsam of Tolu, as well as being synthesized as a solvent and preservative. BA is synonymous with; alpha-hydroxytoluene, alpha-toluenol, phenylmethanol, benzenecarbinol, benzenemethanol, phenylmethyl alcohol, and phenylcarbi-

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nol. It is an aromatic preservative with anesthetic and antipruritic actions. BA is used as a solvent and as a preservative in topical steroids, perfumes, and injectable medications including steroids, vitamin B_{12}, and heparin.

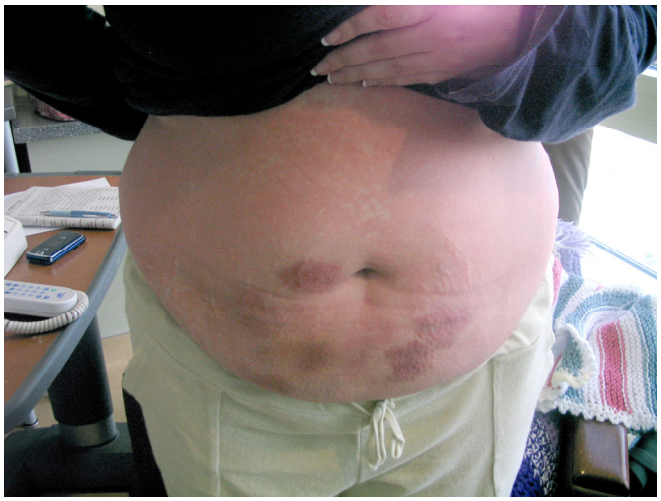

Fig. (1). A 32-year-old female with a history of injection site reaction to benzyl alcohol.

There are reports of serious effects including central nervous system dysfunction, coma, and death in premature infants who have received benzyl alcohol in medications administered intravenously [8-11]. However, as BA was administered intravenously in high doses, the effects observed in premature infants have been somewhat disregarded and the use of BA has still been considered safe at the intended use level.

Allergic contact dermatitis from BA is well known and is on many lists of recommended patch test lists for preservatives [12-16]. It is however not one of the 29 standardized allergen on the T.R.U.E. Test that is most extensively utilized in America. A multicenter dermatologic study in Europe performed testing of 2166 individuals, and found 7 patients tested positive to BA, which amounts to 0.3% hypersensitivity [17]. However, a negative patch test to BA does not exclude sensitization to it [18]. It is much better appreciated that it is an allergen with injectable vitamin B_{12} preparations than steroids because the latter's anti-inflammatory effect masks the allergic reaction [18-20].

Of note, benzyl alcohol is used in several heparin products including heparin lock flush solution. The low molecular weight heparins are not free of this problem. For example, enoxaparin (Lovenox) states that it is preservative-free, yet one of its constituents is benzyl alcohol.

Given the ubiquitous use of heparin as an anticoagulant in medicine and high concern for safety issues related to this drug, it behooves us to make sure that what appear to be heparin allergies are not, in reality, reactions to its preservative.

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