

Hypersensitivity Reactions to Insulins and its Management

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Received: April 07, 2019; **Published:** May 29, 2019

Abstract

Various hypersensitivity reactions may develop during insulin treatment in diabetic patients. These reactions may result from insulin itself or ingredients in the formulation. Hypersensitivity reactions to insulin are rare. However, some types of reactions can be serious and even life-threatening. Diagnosis and treatment of insulin allergy require multidisciplinary cooperation of endocrinology and allergy-immunology specialists.

Keywords: *Insulin Allergy; Diabetes Mellitus; Immediate Hypersensitivity Reactions; Delayed Reactions*

Introduction

Diabetes mellitus (DM) is a common public health problem affecting millions of people worldwide with increasing incidence [1]. All patients with Type 1 DM and many patients with type 2 DM require insulin, while insulin allergy affects 0.1 - 3% of insulin-treated diabetics of all age groups, which may have a significant impact on patients' health [2]. It may develop against insulin itself or additives (protamine, zinc, cresol) present in the preparation [3] and presents mostly as IgE-mediated (type 1) hypersensitivity reactions, although type 3 and type 4 reactions have also been reported [4]. Clinical findings, identification and management of hypersensitivity reactions to insulin formulations are discussed in this topic review.

Discussion

Symptoms of insulin allergy may range from localized itching and rash to serious anaphylaxis [3,5,6] and may begin within 1 hour after injection or later, depending on the type of reaction. In case of localized skin site changes, injection site irritation must be differentiated from insulin hypersensitivity. Injection site reactions may be prevented by optimizing injection technique. Hypersensitivity reactions are categorized as immediate or delayed type reactions (Figure 1). IgE mediated immediate reactions generally develop within 1 hour after injection and may present itself as local reactions (erythema or pruritic wheal at injection site) or more generalized and serious systemic symptoms (urticaria, generalized itching, rhinitis, bronchospasm, angioedema, anaphylaxis) [7-9]. Delayed reactions develop after 1 hour of injection and mostly present as local eczematous or nodular skin changes, which are usually non-life threatening. If symptoms change over time and localized symptoms turn to be more systemic, careful evaluation is required. Type 1 hypersensitivity reactions generally begin months-years after the initiation of insulin therapy (sensitization period is required to form insulin specific IgE), although it is possible to observe reactions beginning after first few injections [3,10]. Pre-formed insulin specific IgE binds to receptors on the surface of mast cells and basophils, which release histamin and other mediators after binding of culprit agent to these immunoglobulins, causing vasodilation and clinical symptoms. Since type 1 hypersensitivity reactions might be serious and life threatening, these patients must be referred to allergy specialists. In this case, culprit insulin should be discontinued and may be substituted with an alternative preparation or an insulin analogue (especially in the subjects allergic to human insulin) if continuation of insulin is required [11], although this may be problematic for those with allergy to additives as additives are present in both human insulin and insulin analogues [12]. Common

additives used in insulin preparations which have been reported to cause type 1 hypersensitivity reactions are protamine sulfate, cresol and latex. Protamine sulfate is a protein added to insulin to delay its absorption, therefore, most long acting insulin preparations contain protamine as additive [13]. Cresol and latex are complexed to insulin as preservatives and may also cause immediate type reactions [14,15]. The diagnosis of type 1 reactions to insulin is based on past and present symptoms and signs, together with skin tests for insulin and additives (either skin prick test or intradermal test) and specific immunoglobulin E (IgE) measurement in the serum for insulin, latex and protamine [16]. Skin prick test is the first step of skin tests and performed by using non-diluted insulin preparations and a wheal diameter of ≥ 3 cm is accepted as positive. In case of negative prick test, further evaluation is performed by intradermal test in which diluted solutions are applied with increasing concentrations [17]. Detection of specific IgE in the serum is also helpful. Diagnostic and therapeutic work-up of insulin allergy is presented in figure 2. Following confirmation of immediate type reaction, management of insulin allergy consists of switching insulin preparation in case of the presence of an insulin preparation that can be used safely or avoiding insulin use when possible. Some patients, however, are insulin dependent and experience symptoms during treatment with many different insulins (Table 1). These patients are difficult to treat and require a more comprehensive approach, sometimes including desensitization [18]. Insulin desensitization is carried out by allergy specialists and is usually well-tolerated and effective in most patients [19]. During desensitization protocol, gradually increasing doses of culprit agent are administered to induce anergy, while blood glucose levels are carefully monitored during the procedure. Delayed reactions to insulins start at least 1 hour and sometimes days after injection. They are usually local and transient, occurring in the form of induration, subcutaneous nodules and eczematous skin changes. In most cases, topical therapies or oral antihistaminic agents are sufficient to resolve symptoms [4]. In unresponsive cases, referral to an allergy or dermatology specialist may be required to perform late-reading skin test or patch test for diagnosis and if a specific allergen causing the reaction is demonstrated, then, insulin preparation lacking this component may be given instead [19].

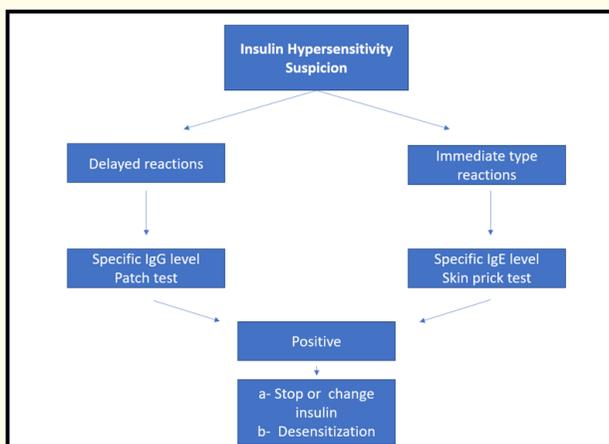


Figure 1: A diagnostic algorithm for patients with insulin allergy.

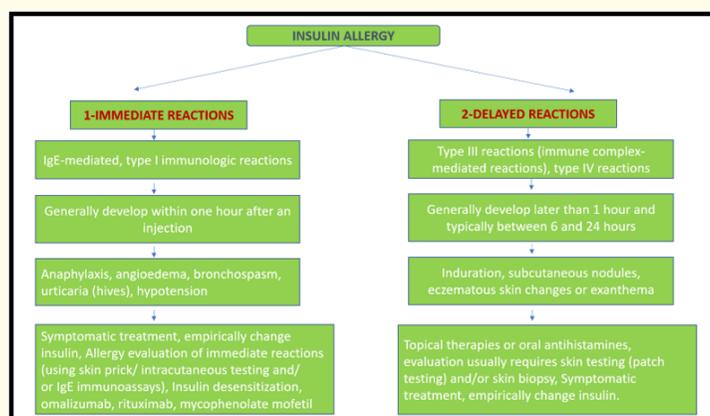


Figure 2: Types of insulin allergy.

Insulin	Type	Clinically Relevant Nonmedicinal Ingredients
Apidra® (Insulin Glulisine)	Short-acting Recombinant Human Insulin Analogue	M-cresol, trometamol, sodium chloride, polysorbate, water for injection, hydrochloric acid, sodium hydroxide
NovoRapid® (Insulin Aspart)	Short-acting Recombinant Human Insulin Analogue	Disodium phosphate dihydrate, glycerol, hydrochloric acid, metacresol, phenol, sodium chloride, sodium hydroxide, zinc chloride solution, water for injection
Humalog® (Insulin Lispro)	Short-acting Recombinant Human Insulin Analogue	Glycerin, dibasic sodium phosphate, metacresol, zinc, phenol, water for injection, hydrochloric acid and/or sodium hydroxide
Humulin R® (Insulin Regular)	Short-acting Biosynthetic Human Insulin Analogue	Glycerol, m-cresol, water for injection, hydrochloric acid and sodium hydroxide
Actrapid® (Human insulin)	Short-acting human insulin preparation	Glycerol, meta-cresol, zinc chloride, water for injections, hydrochloric acid and sodium hydroxide
Levemir® (Insulin detemir)	Long-acting Recombinant Human Insulin Analogue	Zinc, m-cresol, mannitol, phenol, disodium phosphate dihydrate, sodium chloride, water for injection, hydrochloric acid and/or sodium hydroxide
Lantus® (Insulin glargine)	Long-acting Recombinant Human Insulin Analogue	Zinc, m-cresol, glycerol, polysorbate, water for injection, hydrochloric acid and sodium hydroxide
Humulin® N (NPH)	Long-acting Recombinant Human Insulin (rDNA Origin)	Protamine sulfate, glycerin, dibasic sodium phosphate, metacresol, phenol, zinc, water for Injection, sodium hydroxide and/or hydrochloric acid

Table 1: Insulin types and clinically relevant nonmedicinal ingredients.

Conclusion

Diagnosis and treatment of insulin allergy requires multidisciplinary cooperation of endocrinology and allergy-immunology specialists.

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Volume 4 Issue 4 June 2019

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