CASE REPORT
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Successful Treatment of Insulin Allergy with Desensitization Therapy: A Case Report and Literature Review

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ABSTRACT

Insulin therapy is an essential treatment for type 1 and uncontrolled type 2 diabetes mellitus (DM). Hypersensitivity reactions have been described since the first administration of insulin, the same as any other therapy. Despite being a rare situation nowadays, it requires careful intra-hospital monitoring and multidisciplinary management. Here, we present a case of a 57-year-old patient with type 2 DM, an average glycemic control, and both penicillin and insulin allergy. Heunderwent a desensitization protocol which allowed successfully dismiss him with intermediate-acting insulin.

Keywords: Desensitization, Immunologic; Diabetes mellitus; Hypersensitivity; Insulin

INTRODUCTION

Type 2 diabetes mellitus (DM) is a chronic disease characterized by a combination of reduced insulin secretion by pancreatic beta cells and a peripheral insulin resistance. The use of insulin therapy in type 2 DM is a part of the natural history of the disease.[1]

Insulin is known to have several side effects including hypersensitivity reactions. In 1922, the first usage of insulin extracted from animal islet cells caused a callus at the injection site.[2] After the introduction of the highly-purified animal insulin in the 1970s and Human insulin in 1978, the hypersensitivity reactions dramatically decreased from 50% in 1950 to less than 3% in 1990.[3] Currently, the incidence is estimated at <1% to 2.4%.[4]

Both, insulin and the additives in insulin preparations could cause hypersensitivity reactions ranging from minor local symptoms to severe anaphylaxis reactions.

Here, we report a case of insulin allergy that was successfully desensitized using NPH (neutral protamine Hagedorn)-based protocol, in addition to reviewing case reports found in Pubmed from 1997 to July 2017 using the following terms: "Hypersensitivity, Immediate"[Mesh] AND "Insulin"[Mesh] AND (Case Reports[ptyp] AND "humans"[MeSH Terms]) and the ones reported by S. Hasani-Ranjbar et al.[5]

CASE REPORTS

A 57-year-oldman with T2DM was referred to our Endocrinology Diabetology Department due to hypersensitivity manifestations that appeared a few minutes after each insulin injection.

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The patient had an only significant history of allergy to penicillin. In his familial history, we found several members with Type 2 DM (T2DM), hypertension, early atherosclerotic cardiovascular disease and autoimmune diseases including Type 1DM and hypothyroidism.

His diabetes was discovered 20 years ago, treated for two days by insulin then he was dismissed with oral anti-diabetic medication (OAD).

The patient was undergoing an irregular follow-up with poor glycemic control and HbA1c between 11.6% - 14% during the last few years. In order to achieve better glycemic control, the insulin therapy was initiated two years ago and the patient received subcutaneous injections of 10 IU bed-time of NPH insulin (Insulatard, strength: 100 IU/mL, Novo Nordisk, Bagsvaerd, Denmark) in addition to metformin 850 mg twice a day (b.i.d) and glimepiride 4 mg once a day (o.d).

The NPH was taken irregularly due to generalized pruritus and papular lesion located at the insulin injection site that was described since the first usage. The symptoms started ten minutes after the injection and disappear after a few hours. The same manifestations recurred after each injection.

Few weeks before his admission, He received a 10 IU bed-time of biphasic insulin aspart (Novomix30 FlexPen, 100 IU/mL, Novo Nordisk, Bagsvaerd, Denmark) without significant improvement.

The admission exam in October 2016 found a patient with 181 cm Height, 76 kg weight, 95 cm waist size, a body mass index of 23 kg/m2 and a newly discovered hypertension treated by an Angiotensin-converting enzyme (ACE) inhibitor (Captopril 25 mg t.i.d). Diabetes autoantibodies were negative including Anti-GAD, anti-IA2, and anti-ICA antibodies. The biochemical evaluation revealed TSH and FT4 values in the normal references range 1.58 mIU/L and 15 [12-22 pmol/L] respectively and an elevated total Ig E dosage at 173 IU/ml [normal value < 150 IU/mL].

The treatment was switched to glargine (Lantus SoloStar, 100 IU/mL, Sanofi, Frankfurt, Germany) and the patient received 8 IU without premedication. A papule appeared ten minutes after the injection and disappeared after fifteen minutes without pruritus. The patient received after thatH1 antagonist (cetirizine 10 mg q.d.) during 4 days followed by an injection of rapid-acting insulin (Jusline R, 100 IU/mL, Julphar, Ras Al Khaimah, U.A.E) that caused also a papular lesion without pruritus.

Since the patient presented hypersensitivity to different insulin preparations a desensitization protocol was planned after three months. The patient was dismissed with a satisfying glycemic control using glimepiride 2 mg o.d and metformin 850 mg b.i.d in addition to lifestyle management with fasting plasma glucose equal to 118 mg/dL and postprandial plasma glucose under 186 mg/dL.

In February 2017, during the second admission, the patient showed a suboptimal glycemic control with HbA1c equal to 7.7% and a stable weight. We tried first glulisine (Apidra Solostar, 100 UI/mL, Sanofi, Frankfurt, Germany) which contains essentially metacresol in addition to insulin which was stopped after the third injection since a papular lesion occurred again (Figures 1 and 2).

Due to the unavailability of specific IgE assay and skin tests, we tried to eliminate differential diagnosis especially dermographism and allergy to the components of the syringe. Applying pressure and friction to the skin, changing the needle, the injection site, verifying the injection procedure and injecting subcutaneously isotonic saline using the insulin syringe did not induce any allergic symptoms. We also tried to eliminate a possible metacresol allergy by giving subcutaneous injections of Test Medium FlexPen (Novo Nordisk, Bagsvaerd, Denmark) which does not show any allergic manifestation.

The patient underwent after that a desensitization protocol using progressive doses of NPH (Jusline N, 100 IU/mL, Julphar, Ras Al Khaimah, UAE) associated with an H1 antagonist (cetirizine 10 mg q.d.) and corticosteroid (Table 1).

He did not present any hypersensitization symptoms during this procedure even after stopping the premedication. He was dismissed with NPH 10 IU twice a day. Eight months after the desensitization, we obtained a satisfying glycemic control without recurrence of insulin allergy symptoms.

Figure 1. A papular lesion appearing 10 minutes after the third injection of glulisine in a 57-year-old patient with diabetes mellitus type 2

Figure 2. The papular lesion starting to fade after 1 hour and 30 minutes of the third injection of glulisine in a 57-year-old patient with diabetes mellitus type 2

Table 1. Desensitization protocol using neutral protamine Hagedorn (NPH) insulin in a 57-year-old patient with diabetes mellitus type 2 and insulin allergy

Day	Time	Premedication	Insulin dose (IU)
1	-30 min	H1 + 60 mg prednisone	
	0		0.001
	20 min		0.01
	40 min		0.1
	60 min		1
	80 min		2
2	-30 min	H1 + 30 mg prednisone	
	0		0.1
	20 min		1
	40 min		2
	60 min		3
3	-30 min	H1 + 30 mg prednisone	
	0		2
	20 min		3
	40 min		4
4	-30 min	H1 (+ stop prednisone)	
	0		5
	20 min		6
5	-30 min	H1	
	0		6
	20 min		8
6	-30 min	H1	
	8 AM		6
	8 PM		8
7	-30 min	H1	
	8 AM		8
	8 PM		10
8	8 AM	(Stop H1)	10
	8 PM		10

DISCUSSION

Insulin allergy is as a rare condition that could be related to the components of insulin preparations mainly protamine,[2] zinc[6,7] and metacresol[4,8,9] or in less than one-third of cases related to insulin itself.[2] Its incidence dropped significantly after the introduction of the highly-purified animal insulin and the use of recombinant human insulin.[3]

The manifestations may be type I IgE-mediated hypersensitivity, type III immune complex-mediated hypersensitivity or type IV delayed hypersensitivity. The reactions can vary from simple local reactions to a life-threatening anaphylactic reaction.[10]

In order to confirm insulin allergy, the differential diagnosis should be excluded mainly skin diseases and an incorrect injection technique. U. Bodtger found that 59% of suspected cases did not have an allergic cause.[11]

In our case, the patient presented a type 1 IgE-mediated hypersensitivity with local, general manifestations and a high total IgE value. The dermatologic disease was eliminated, the injection technique was correct, the injection of isotonic saline solution using insulin syringe did not show any reaction eliminating a possible allergy to its components such as latex. The patient had a known history of allergy to penicillin which is reported to have a high prevalence in patients with insulin allergy.[12]

Hypersensitivity reactions occur usually a few weeks, months or years after the onset of insulin therapy.[13] In our case, it happened since the first injection which could be explained by his previous exposure to insulin.

We tried glargine since the insulin allergy was less frequent with insulin analogs, also glargine could be used as a desensitization treatment,[5] however, the dose delivered to the patient was higher than the one required to start desensitization.

The patient presented hypersensitization to multiple insulin preparations including NPH, soluble insulin, biphasic insulin aspart, glargine, glulisine. The only common components existing in these preparations that were reported to cause allergy are metacresol and insulin (Table 2).[3]

Allergy to metacresol was reported previously in the literature, and in order to eliminate a possible metacresol allergy, we used Test Medium FlexPen which contains metacresol and phenol without insulin. This procedure was used previously by B.J. Wheeler to prove the metacresol allergy.[4]

Since the insulin allergy was confirmed and considering the patient age, the natural history of type 2 DM and the suboptimal glycemic control, we decided after the patient agreement to realize a desensitization protocol, similar to the one used by Rojas J,[10] which was successful.

Table 2. Insulin preparations and its components

Brand Name	Insulin	Protamine	Zinc	Metacresol
Actrapid®	human Insulin rDNA		X	X
Insuman rapid®	human Insulin rDNA			X
Jusline R®				
Insulatard®	human Insulin rDNA	X	X	X
Insuman basal®				
Jusline N®				
Mixtard $_{30/70}$®	human Insulin rDNA			
Insuman comb$_{30/70}$®		X	X	X
Jusline $_{30/70}$®				
Novomix $_{30}$®	biphasic insulin asparte	X	X	X
Novorapid flexpen®	asparte		X	X
Apidra solostar®	glulisine			X
Levemir flexpen®	detemir		X	X
Lantus solostar®	glargine		X	X

rDNA: recombinant DNA

The patient was allowed to receive metformin but glimepiride was prescribed only during the first four days considering the high dose of Prednisone. Although corticosteroids were used in desensitization protocols mainly when general symptoms were present, some authors used it concomitantly with insulin in local manifestations.[14]

We found from 1997 to July 2017, 33 similar cases with immediate hypersensitivity reactions to different insulin types with a sex ratio of 1.06, 66.7% (n=22) type 2 DM patients, 24.2% (n=8) type 1 DM and 3 specific DM. The management of insulin allergy varied from interrupting the insulin therapy and resuming the OAD medications, keeping the same treatment or the same class and adding H1 antagonist, trying the type of insulin that showed the least reaction in the skin tests or using a desensitization protocol. The desensitization was done in 57.6% of cases (n=19) and a recurrence of symptoms was seen in 15.8% of cases only (n=3).

In case of unsuccessful desensitization, other options could be used including systemic steroids, immunosuppressive agents such as azathioprine, mycophenolate mofetil, and methotrexate, targeted biologic agents such as rituximab and omalizumab or even pancreas transplantation in case of generalized insulin allergy[15-45](Table 3).

Table 3. Cases with an immediate insulin hypersensitivity

Author/Reference	Year	Age (years)	Sex	Type of DM	Duration of DM	Type of Insulin	Desensitization	Treatments	Results	Duration of follow-up	Recurrence	Otherhypersensitivity agents
Belhekar M.N. (15)	2015	41	Female	2	2 years	Soluble insulin & NPH	No	glargine	No reaction	-	No	penicillin and pentoxifylline
Pitrola D. (16)	2014	48	Male	2	-	Biphasic insulin lispro, biphasic insulin aspart & glargine	No	Stopped statin and ACE inhibitor and reintroduced glargine after 9 months	No reaction	6 weeks	No	-
Jacquier J. (17)	2013	65	Male	secondary to total pancreatectomy	1.5 years	NPH & lispro	No	detemir, lispro & H1 antagonist	No reaction	4 weeks	No	No
Jacquier J. (17)	2013	40	Female	1	4 months	glargine, lispro, detemir & aspart	No	aspart/continuous subcutaneous insulin infusion & H1 antagonist	Mild symptoms	3 weeks	No	Animal dander, pollen, family history of atopy
Jacquier J. (17)	2013	49	Female	2	19 years	Soluble insulin & NPH	No	Insulin discontinued and oral hypoglycemic agents resumed	No reaction	-	No	Sulpha drugs, family history of seasonal allergies

Hasselmann C. (18)	2013	8	Male	1	3 months	protamine, NPH, aspart, glargine & lispro	Yes	lispro/Continuous subcutaneous insulin infusion & H1 antagonist	Mild symptoms	3 years	No	-
Yoshida N. (19)	2012	44	Female	Secondary to hemochromatosi	12 years	Soluble insulin & lispro	No	aspart & prednisolone (used for acute then chronic graft-versus-host disease)	Skin reactions which disappeared after 7 years	7 years	No	-
Hasani-Ranjba S. (5)	2012	55	Female	2	12 years	Soluble insulin & NPH	No	glargine& H1 antagonist then aspart	No reaction	3 months	No	Mild intermittent asthma & allergic rhinitis
Luyasu S. (20)	2011	50	Male	2	-	NPH & protamine	Yes	Soluble insulin then asparte & glargine	No reaction	2 years	No	-
Tuboi M. (21)	2010	43	Male	2	10 years	Multiple insulin preparations	Yes	glargine	Mild local symptoms	6 month	No	No
Wang C. (22)	2009	63	Male	2	17 years	NPH, soluble insulin, premixed human insulin & lispro	No	Insulin discontinued and oral hypoglycemic agents resumed	No reaction	1 month	No	-
Hara M. (23)	2009	56	Male	2	10 years	NPH	Yes	Glargine, aspart & H1 antagonist	No reaction	3 weeks	No	-
Caruso C. (24)	2009	65	Female	2	-	Soluble insulin	No	Insulin discontinued and oral hypoglycemic agents resumed	-	-	No	penicillin
Pérez E. (25)	2009	79	Male	2	10 years	detemir	No	glargine & glulisine	No reaction	-	No	-

Mollar-Puchades MA. (12)	2009	70	Male	2	20	NPH, biphasic insulin Aspart, Biphasic insulin lispro, Insulin Lispro Protamine & soluble insulin	No	glargine & glulisine	No reaction	-	No	penicillin
Pföhler C. (26)	2008	68	Male	2	-	Every insulin preparation	Yes	Ultra-rush desensitization protocol: human insulin then glargine & H1 antagonist	No reaction	6 months	No	-
Neville KA. (27)	2008	9	Male	1	1 year	Soluble insulin & NPH	Yes	lispro/continuous subcutaneous insulin infusion & H1 antagonist	Mild symptoms	15 months	No	Eczema/asthma, peanut (anaphylaxis), kiwifruit (urticaria)
Neville KA. (27)	2008	9	Male	1	6 months	Soluble insulin & NPH	Yes	lispro/continuous subcutaneous insulin infusion & H1 antagonist	Mild symptoms	15 months	No	Allergic rhinitis, eczema
Kaya A. (28)	2007	46	Female	2	17 years	Soluble insulin & NPH	Yes	Soluble insulin	Anaphylactic reaction	Patient had died	-	No
Madero M.F. (29)	2006	35	Female	1	28 years	Recombinant human insulin/glargine	No	lispro	No reaction	7 years	No	-

Moyes V. (30)	2006	60	Male	2	11 years	glargine, premixed human insulin, Biphasic insulin lispro & biphasic insulin aspart	Yes	lispro/continuous subcutaneous insulin infusion	Mild local reactions	-	No	-
Katahira M. (31)	2005	56	Male	2	20 years	Soluble insulin & premixed human insulin	No	Soluble insulin	No reaction	6 years	No	No
Matheu V. (32)	2005	25	Male	1	3 years	NPH, lispro, soluble insulin & protamine	Yes	aspart/continuous subcutaneous insulin infusion & corticosteroids	No reaction	6 years	No	-
Kara C. (33)	2005	1	Female	Neo-natal diabetes	1 year	NPH & soluble insulin	Yes	1st essay: soluble insulin 2nd essay: lispro & glargine	1st: not successful	6 months	No	No
Adachi A. (34)	2004	66	Female	2	5 year	NPH	No	Human insulin extended zinc suspension	No reaction	3 years	No	Pollinosis
Rauben-heimer PJ. (35)	2004	57	Male	2	10 year	Premixed human insulin & soluble insulin	Yes	Soluble insulin & H1 antagonist	Allergic symptoms recurred	> 2 weeks	Yes	No

Baur X. (36)	2003	63	Femal	2	9 year	NPH, premixed human insulin & protamine	No	Insulin discontinued	-	-	No	No
Barranco R. (37)	2003	62	Male	2	10 year	Biphasic insulin lispro	Yes	Soluble insulin then lispro & H1 antagonist	Mild local reactions	6 months	Yes	extrinsic asthma and urticaria by pyrazolones
Yokoyama H. (14)	2003	64	Male	2	15 years	Premixed human insulin, crystalline zinc-insulin & protamine	Yes	Crystalline zinc-insulin & corticosteroids	No reaction	6 months	No	-
Rosas Vargas MA. (38)	2001	13	Female	1	4 years	recombinant DNA insulin	Yes	Soluble insulin & H1 antagonist	No reaction	14 months	No	-
Nagai Y. (39)	2001	81	Male	2	32 years	Soluble insulin, NPH & protamine	No	Insulin discontinued and oral hypoglycemic agents resumed	No reaction	> 2 weeks	No	No
Sackey AH. (40)	2001	6	Male	1	1 year	Premixed human insulin	No	Premixed human insulin & H1 antagonist	Confined with mild local reactions	2 years	Yes	No
Pánczél P. (41)	2000	54	Female	2	32 years	NPH (immediate reaction) & protamine (delayed reaction)	No	lispro & bedtime sulfonylurea treatment	No reaction	-	No	Adverse reactions to chromium, pollen, dust, penicillin, acarbose, and metformin

Bollinger ME. (42)	1999	19	Female	1	14 years	Soluble insulin & NPH	Yes (4 times)	H1 antagonist & corticosteroids 1st essay: soluble insulin 2nd essay: soluble insulin 3rd: soluble insulin & NPH 4th: soluble insulin and stopping NPH	1st: Allergic symptoms recurred after a few weeks 2nd: similar results 3rd: intermittent hives	3 years	Yes	-
Gonzalo MA. (43)	1998	32	Female	1	4 months	Soluble insulin & premixed human insulin	No	Same & H1 antagonist	Mild local reactions	-	Yes	No
Nagai T. (44)	1997	63	Female	1	4 months	NPH	Yes	Soluble insulin/ continuous subcutaneous insulin infusion	No reaction	305 days	No	No

NPH: neutral protamin Hedghorn, ACE: angiotensin-converting enzyme

We reported here an unusual case of allergy to both penicillin and to multiple insulin preparations which were successfully handled by a desensitization protocol using NPH insulin.

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