

A rational clinical approach to suspected insulin allergy: status after five years and 22 cases

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Abstract

Aims Allergy to recombinant human (rDNA) insulin preparations is a rare complication of insulin therapy. However, insulin preparations contain several allergens, and several disorders can resemble insulin allergy. Studies evaluating the diagnostic procedures on suspected insulin allergy are extremely few.

Methods Since January 1998, we have used a standardized investigative procedure during admittance to the medical ward allowing observation and repeated recording of reactions to intradermal skin test (performed with a commercially available kit containing isolated insulin allergens). Data on all investigated cases until April 2003 were collected retrospectively, and self-reported efficacy of intervention was compared to clinical data.

Results Twenty-two patients were included. In nine (41%) cases, non-insulin allergic causes were discovered and successfully treated: poor injection technique ($n = 5$), skin disease ($n = 3$) and other systemic allergy ($n = 1$). Nine other patients were found to be allergic to protamine ($n = 3$) or rDNA insulin ($n = 6$), and specific treatment was associated with relief in 8 patients (89%). Four patients had local reactions of unknown causes but symptom relief was obtained in three cases by unspecific therapy. Overall, 20 (91%) reported relief of symptoms.

Conclusion Our standardized investigative procedure of suspected insulin preparation (IP) allergy was associated with relief of symptoms in > 90% of patients. IP allergy was diagnosed in 41%, and intradermal testing with isolated insulin allergens was a prerequisite in identification of culprit allergen and targeting of treatment.

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Keywords Insulin; protamine; allergy; diagnosis; skin test

Abbreviations IP, Insulin preparation; rDNA, Recombinant insulin; IDT, Intradermal test

Introduction

Allergic reactions during human recombinant (rDNA) insulin therapy have been reported in several cases [1–14]. The insulin preparation (IP) contains multiple potential allergens: insulin, carrier proteins, and additives [15]. Furthermore, several conditions resemble IP allergy, e.g. epicutaneous injection, other skin disease or systemic allergy, or nonallergic asthma [16]. Recently, a 2.5% annual prevalence of suspected IP allergy in

rDNA insulin treated patients was reported [17]. The diagnostic challenge is evident but only one available paper has yet investigated the diagnostic procedure of suspected rDNA insulin allergy [12]. In the rare cases of 'true' IP allergy, identification of the culprit allergen allows specific targeting of the intervention [16,18,19]. Such identification is possible through intradermal testing (IDT) [20]. A commercially available IDT kit containing several potential IP allergens has been used in case reports [1,4,7,10,21,22].

In the present paper, we report our 5-year experience with a standardized procedure for suspected IP allergy (Fig. 1) in a regional diabetes centre.

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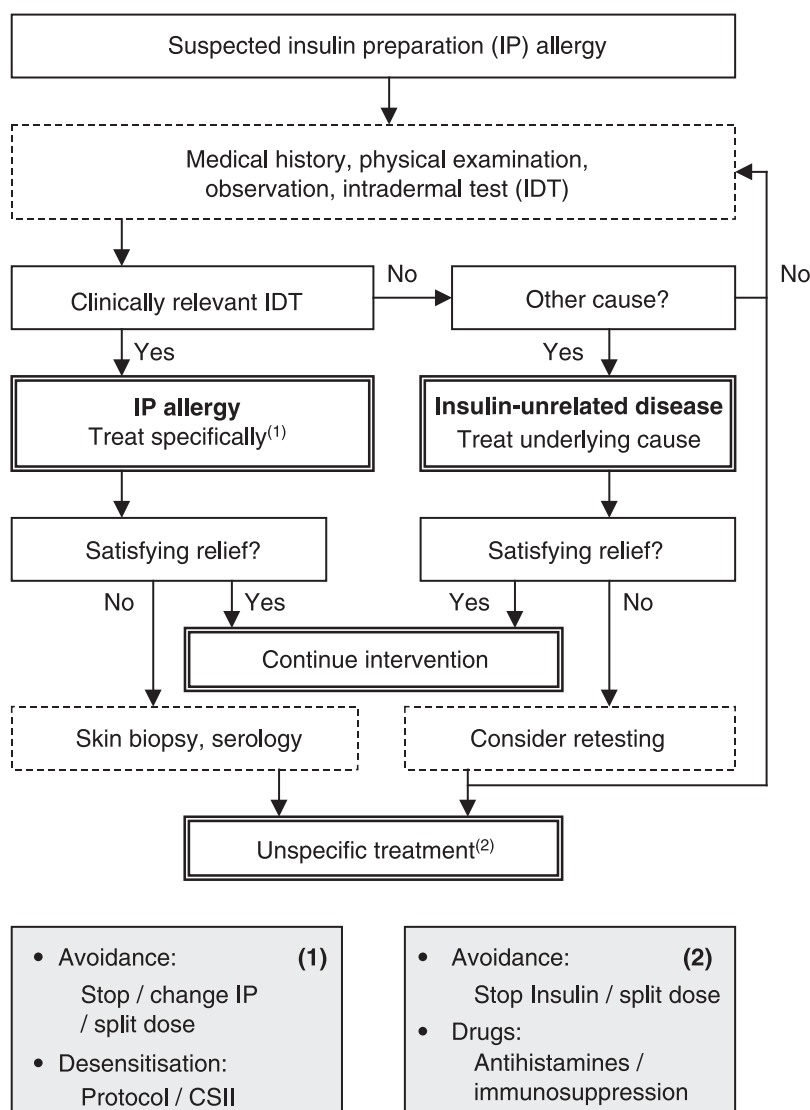


Figure 1 Algorithm for rational investigation and treatment of suspected insulin preparation allergy

Methods

Study design

The study is retrospective, describing the efficacy of a standardized diagnostic procedure for suspected IP allergy (Fig. 1) used since 1 January 1998 at the medical ward, Steno Diabetes Centre (SDC; Copenhagen, Denmark).

Patients

All patients admitted to the ward with suspected IP allergy from January 1998 to April 2003 were included. Medical files were read in June 2003, and relevant data were manually recorded on anonymous data sheets.

Diagnostic procedures including intradermal test (IDT)

Day 1: medical history, physical examination and observation of self-care measures including injection technique. Day 2: IDT

on the anterior forearm at least 3 cm apart (0.05 ml; monoplicate): insulins (regular human, porcine MC and bovine MC, all 5 IU/ml), and media: paraben (methylparahydroxy-benzoate 1 mg/ml), phenol (2 mg/ml), metacresol (3 mg/ml), zinc chloride (50 µg/ml), isophane (disodium phosphate dihydrate 2.4 mg/ml) and protamine sulphate (350 µg/ml) (all: Insulin Allergy Kit; Novo Nordisk, Bagsværd, Denmark). Histamine (0.1 mg/ml) and diluent served as positive and negative control, respectively. The mean of largest orthogonal diameters of wheal, erythema, and induration was recorded at 10, 30, 60, 240 and 1440 min. Positivity (sensitization) was defined as a wheal and/or induration ≥ 0.5 [histamine wheal] [20], but considered clinically irrelevant if not supported by medical history.

Outcome parameters

Primary endpoint: self-reported (binary) efficacy of intervention. Secondary end-point: presence of IP allergy (positive IDT, supportive medical history). Demographic and diabetological

baseline parameters were investigated in relation to these parameters.

Statistics

Data were examined using statistical software (SPSS for Windows, version 11.0, Chicago, IL, USA) with Mann–Whitney *U*-test (continuous data) and Fisher's exact test (categorical data). Significance was reached at $P < 0.05$.

Results

Patients

Table 1 depicts the clinical course of the 22 patients admitted (from SDC outpatient department ($n = 21$), or to SDC because of suspected IP allergy (patient no. 19)) and included in the study. A median of 199 (range: 60–680) days passed between the first day with a suspected IP allergic reaction and allergy testing. Three patients had received non-rDNA insulin: no. 19 (animal insulin) and no. 12, 19, 22 (MC insulin). Patients 12, 19 and 20 were experimentally and unsuccessfully shifted from NPH to zinc insulin while awaiting allergy testing. No patient was intermittently treated with insulin.

Diagnosis

In 9 (41%) patients without relevant skin sensitization other causes of symptoms were found ($n = 5$: poor injection technique; $n = 3$: skin disease; $n = 1$: other allergy). Aimed treatment was successful in all (Table 1). Another 9 patients had IP allergy ($n = 6$: human insulin; $n = 3$: protamine), and specific intervention was successful in 89% ($n = 8$). In the nonresponding patient (no. 22), leucocytoclastic vasculitis was found by dermahistopathological examination and relieved by oral corticosteroids [23]. Four IDT-negative patients (18%) received no specific diagnosis: all experienced persistent mild local symptoms to NPH insulin only (patients no. 9 and 12 received regular insulin, too). The term 'NPH intolerant' was imprecise as avoidance, split dose and systemic antihistamine rather than nonprotamine insulin relieved symptoms.

IDT elicited no systemic reactions or positive skin reactions to the negative control.

Primary and secondary end-points

Overall, 20 (91%) of 22 patients reported relief of symptoms after intervention. We found no significant intergroup differences in base-line parameters (columns 2–9, Table 1) neither when using 'satisfying efficacy of intervention?' (yes/no: $n = 20/2$), or 'specific diagnosis?' (yes/no: $n = 18/4$) as grouping variable. With IP allergy as grouping variable (yes/no: $n = 9/13$), we found that injection site induration was reported significantly more often in insulin allergic subjects (6/9 vs. 2/13, $P < 0.03$). No other significant difference was found (columns 2–9, Table 1)

but self-reported penicillin allergy tended to be reported more often (3/9 vs. 0/12 patients; $P = 0.06$).

Discussion

This retrospective and uncontrolled study indicated that a multidisciplinary diagnostic procedure resulted in the relief of symptoms in 91% (20/22) of patients with suspected allergy to rDNA IP. Being retrospective, our results remain suggestive but will hopefully inspire future prospective studies. We found that 59% of suspected cases did not have an allergic cause. Thus, an uninvestigated insulin allergy diagnosis erroneously stigmatizes nonallergic patients. True insulin allergy is incompatible with insulin dependency but identification of culprit allergen facilitates specific diagnosis and onset of alternative insulin therapy. The relevance of the present paper is strengthened by the fact that it is preceded by only one study [12].

IDT with isolated IP compounds proved to be a relevant method in identification of culprit allergens, thus supporting several case reports [1,4,7,10,21,22]. The interpretation of IDT results was based on clinical findings that were supported in 82% (18/22) of cases. To our knowledge, the diagnostic power of the insulin allergy kit has not been validated in a published clinical study. Unfortunately, our study is too small to provide sufficient evidence for specificity and sensitivity calculations. Non-allergic diabetic subjects can be skin test positive, most often to protamine and less often to rDNA insulin [8,12], but the clinical impact of this asymptomatic sensitization remains to be prospectively investigated, too [24]. In our study, all sensitized patients experienced symptom relief when specific avoidance was initiated. Having a relevant sensitization was independent of gender, age, diabetes type and diabetes duration, but dependent on the clinical picture, induration and penicillin allergy (tendency) [19] was more frequent. Four IDT-negative patients did not achieve a specific diagnosis. NPH insulin resulted in mild, local allergic symptoms, whereas rDNA insulin and thereby latex (present in vial membranes) was accepted. As symptoms remained mild and local, neither serological nor dermahistopathological examination was conducted. The appropriateness of this decision is questionable, as these procedures might have elucidated the type of inflammation: IgE-, IgG- or cell-mediated, which has therapeutic implications [16,25]. Three patients (75%) reported at least partly relief of symptoms after unspecific intervention (Table 1).

Nearly 6500 patients attended our outpatients department in the study period, but calculation of prevalence rates is biased by patient selection, since only patients with persistent (>6 weeks) symptoms were admitted to allergy testing. Recently, a large study ($n = 4512$) identified a 2.5% annual prevalence of patients reporting suspected IP allergy, where half of reported events were considered unrelated to insulin therapy [17]. This leaves a 1.3% annual prevalence of continuously suspected IP allergy, confirming that rDNA IP allergy is significantly more rare than allergy to nonhuman IP [26]. If

Table 1 Patients with suspected insulin preparation allergy shown as cases: background demographic and diabetological data, symptoms, intradermal test, diagnosis, intervention and outcome

Patient no.	Gender	Age (years)	DM Type	Onset (months)	Prior hyper-sensitivity	Symptoms													Time span	Intradermal test							Diagnosis	Intervention	Efficacy		
						Insulin therapy			Local					Systemic																	
						Reg.	Mono.	NPH	Ery.	Wheal	Prur.	Ind.	Pain	Urtic.	Prur.	Urtic.	Asth.	Hum.		Prot.	Met.	Zinc	Isop.	Porc.	Bov.						
1	F	48	2	1	H-f			+	x	—	x	—	—	—	—	—	—	10 m									Poor inj t	S/care	+		
2	M	60	2	2	—			+	x	x	x	—	—	—	—	—	—	24 h									Poor inj t	S/care	+		
3	M	43	1	0.5	—	+		+	x	x	—	—	—	—	—	—	—	3 h									Poor inj t	S/care	+		
4	M	56	2	1	—			+	x	x	x	—	—	—	—	—	—	24 h									Poor inj t	S/care	+		
5	F	55	2	0.5	—			+	x	—	x	—	—	—	—	—	—	1.5 h									Poor inj t	S/care	+		
6	M	68	2	18	H-f			+	—	x	—	x	x	—	x	x	—	0 m									Id. urtic.	S/care/AH	+/+		
7	M	50	2	1	Y-j			+	—	—	—	—	—	—	x	—	—	n.a.							o		Psoriasis	Ref. dermat	+		
8	F	56	2	5	n.i.	+		+	x	—	—	—	—	—	—	—	—	48 h									Nickel	Ref. dermat	+		
9	F	29	1	1	—	+		+	x	—	—	—	x	—	—	—	—	24 h								o	NPH intol.	Split dose	(+)		
10	M	66	2	2	—			+	—	x	x	—	—	—	—	—	—	1 h									NPH intol.	Stop insulin	+		
11	M	59	2	0.5	—			+	x	—	x	—	—	—	—	—	—	5 m									NPH intol.	Analog/AH	–/+		
12	M	41	1	14 years	—	+	+	+	x	—	—	x	x	—	—	—	—	0 m									NPH intol.	Monotard	—		
13	M	61	2	9	ASA			+	—	—	—	—	—	—	x	x	x	n.a.									ASA all.	Stop ASA	+		
14	M	77	2	1	—			+	x	x	x	x	—	—	—	—	—	10 m	x							o	Insulin	Stop insulin	+		
15	F	62	2	1	Pen			+	x	x	x	x	—	—	—	—	—	7 h				x	x				Protamine	Split dose	+		
16	F	62	2	1	—			+	—	x	—	x	x	—	—	—	—	1 h									Protamine	Monotard	+		
17	F	49	1	3	—			+	x	x	x	x	—	—	—	—	—	20 m	o			x				o	o	Protamine	Monotard	+	
18	M	46	2	1	—			+	x	x	x	x	—	—	—	—	—	1 h	x							o	Insulin	Analog	+		
19	M	26	1	2	Pen	+	+	+	—	—	—	—	—	x	x	x	—	48 h	x			x			x	o	o	Insulin	Analog	+	
20	M	34	1	n.a.	H-f	+	+	+	x	x	x	—	—	—	—	—	—	n.a.	x			x			x	x	o	o	Insulin	CSII	+
21	F	67	2	0.5	Pen			+	x	x	x	—	—	—	—	—	—	6 h	x							o	o	Insulin	Analog	+	
22	F	45	1	9 years	—	+		+	x	—	—	x	x	—	—	—	—	4 h	x							o	o	Insulin	Analog/CSII/CS	–/–/+	

n.a. data not available. H-f, hay-fever; Y-j/ASA/Pen, yellow-jacket venom/acytic acid/penicillin allergy. Insulin therapy: Reg. regular, Mono. Monotard, +, insulin preparation used prior to suspected allergy; Symptoms: Ery. erythema, Prur. pruritis, Ind. induration, Urtic. urticaria, Asth. asthma, x, symptoms present, – , symptoms absent; Intradermal test: Hum, rDNA insulin; Prot, protamine sulphate; Met, metacresal; Isop, isophane; Porc, porcine MC insulin; Bov, bovine MC insulin; x/o/–, positive relevant/positive irrelevant/negative result. Data for parabens or phenol not shown as no positive reactions were induced; Diagnosis: Poor Inj t, poor injection technique; Id, idiopathic; Intol, intolerance; Insulin or Protamine, culprit allergen; Intervention: S/care, selfcare education; Ref dermat, referred to dermatologist; AH/CSII/CS, antihistamine/continuous subcutaneous insulin injection/systemic corticosteroid therapy; Efficacy: + / (+) / – , satisfying / dissatisfying / no improvement.

this prevalence is representative, one case of suspected insulin allergy occurs for every 76 insulin treated patients (1/1.3%), thus it is highly probable that every diabetologist will encounter suspected IP allergy.

Overall, our results suggest that an investigative procedure (presented as an algorithm, Fig. 1) including careful history taking, physical examination, observation of self-care measures, and IDT with a commercially available insulin allergy kit provides the clinician with sufficient relevant information to initiate specific intervention resulting in relief of symptoms in 90% of patients. Our presented diagnostic procedure needs confirmation in larger, prospective studies.

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References

- 1 Takata H, Kumon Y, Osaki F, Kumagai C, Arai K, Ikeda Y, Suehiro T *et al.* The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care* 2003; **26**: 253–254.
- 2 Yasuda H, Nagata M, Moriyama H, Fujihira K, Kotani R, Yamada K, Ueda H *et al.* Human insulin analog insulin aspart does not cause insulin allergy. *Diabetes Care* 2001; **24**: 2008–2009.
- 3 Pratt EJ, Miles P, Kerr D. Localized insulin allergy treated with continuous subcutaneous insulin. *Diabet Med* 2001; **18**: 515–516.
- 4 Panczel P, Hosszufalusi N, Horvath MM, Horvath A. Advantage of insulin lispro in suspected insulin allergy. *Allergy* 2000; **55**: 409–410.
- 5 Bollinger ME, Hamilton RG, Wood RA. Protamine allergy as a complication of insulin hypersensitivity: a case report. *J Allergy Clin Immunol* 1999; **104**: 462–465.
- 6 Gonzalo MA, De Argila D, Revenga F, Garcia JM, Diaz J, Morales F. Cutaneous allergy to human (recombinant DNA) insulin. *Allergy* 1998; **53**: 106–107.
- 7 Nagai T, Nagai Y, Tomizawa T, Mori M. Immediate-type human insulin allergy successfully treated by continuous subcutaneous insulin infusion. *Intern Med* 1997; **36**: 575–578.
- 8 Blanco C, Castillo R, Quiralte J, Delgado J, Garcia I, de Pablos P, Carrillo T. Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. *Allergy* 1996; **51**: 421–424.
- 9 Alvarez-Thull L, Rosenwasser LJ, Brodie TD. Systemic allergy to endogenous insulin during therapy with recombinant DNA (rDNA) insulin. *Ann Allergy Asthma Immunol* 1996; **76**: 253–256.
- 10 Takuma H, Kawagishi T, Kyogoku I, Okuno Y, Nishizawa Y, Morii H. A case of primary and generalized allergy to human insulin with no history of any prior insulin exposure. *Diabetes Res Clin Pract* 1995; **30**: 69–73.
- 11 Towse A, O'Brien M, Twarog FJ, Braimon J, Moses AC. Local reaction secondary to insulin injection. A potential role for latex antigens in insulin vials and syringes. *Diabetes Care* 1995; **18**: 1195–1197.
- 12 Lee AY, Chey WY, Choi J, Jeon JS. Insulin-induced drug eruptions and reliability of skin tests. *Acta Derm Venereol* 2002; **82**: 114–117.
- 13 Saccabusi S, Boatto G, Asproni B, Pau A. Sensitization to methyl methacrylate in the plastic catheter of an insulin pump infusion set. *Contact Dermatitis* 2001; **45**: 47–48.
- 14 Jolanki R, Kanerva L, Estlander T, Henriks-Eckerman ML, Suhonen R. Allergic contact dermatitis from phenoxyethoxy ethylacrylates in optical fiber coating, and glue in an insulin pump set. *Contact Dermatitis* 2001; **45**: 36–37.
- 15 Grammer L. Insulin allergy. *Clin Rev Allergy* 1986; **4**: 189–200.
- 16 Galloway JA, deShazo RD. Insulin chemistry and pharmacology; insulin allergy, resistance, and lipodystrophy. In Rifkin H, Porte D Jr eds. *Ellenberg and Rifkin's Diabetes Mellitus—Theory and Practice*. New York: Elsevier, 1990: 497–513.
- 17 Fineberg SE, Huang J, Brunelle R, Gulliya KS, Anderson JH Jr. Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. *Diabetes Care* 2003; **26**: 89–96.
- 18 Gruchalla RS. 10. Drug allergy. *J Allergy Clin Immunol* 2003; **111**: S548–S559.
- 19 Jegasothy BV. Allergic reactions to insulin. *Int J Dermatol* 1980; **19**: 139–141.
- 20 Dreborg S. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989; **44**: 13–59.
- 21 Gin H, Aubertin J. Generalized allergy due to zinc and protamine in insulin preparation treated with insulin pump. *Diabetes Care* 1987; **10**: 789–790.
- 22 Abdu TAM, Wilkins J, Yelland M, Scarpello JHB. Generalised allergic reaction to human insulin. *Pract Diabetes Int* 2000; **17**: 31–32.
- 23 Mandrup-Poulsen T, Molvig J, Pildal J, Rasmussen AK, Andersen L, Skov BG, Petersen J. Leukocytoclastic vasculitis induced by subcutaneous injection of human insulin in a patient with type 1 diabetes and essential thrombocytemia. *Diabetes Care* 2002; **25**: 242–243.
- 24 Bodtger U, Poulsen LK, Malling HJ. Asymptomatic skin sensitization to birch predicts later development of birch pollen allergy in adults: a 3-year follow-up study. *J Allergy Clin Immunol* 2003; **111**: 149–154.
- 25 deShazo RD, Boehm TM, Kumar D, Galloway JA, Dvorak HF. Dermal hypersensitivity reactions to insulin: correlations of three patterns to their histopathology. *J Allergy Clin Immunol* 1982; **69**: 229–237.
- 26 Scherthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993; **16**: 155–165.