

## Case Report

# Severe Insulin Allergy After Percutaneous Transluminal Coronary Angioplasty

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## ABSTRACT

**Background:** Insulin therapy is essential for type 1 and inadequately controlled type 2 diabetic patients. Insulin allergies have become less common since the introduction of highly purified human recombinant insulin. There are rare reports of severe insulin allergic reactions after percutaneous transluminal coronary angioplasty (PTCA) in patients with type 2 diabetes who had no previous allergic reactions. To better understand the causes and presentation of this rare acute reaction, we present the following observed case.

**Case summary:** A 63-year-old Chinese man (height, 172 cm; weight, 68.5 kg) with a 17-year history of type 2 diabetes and hypertension was first admitted to the West China Hospital, Sichuan University, Sichuan, People's Republic of China, for uncontrolled type 2 diabetes. He used regular human insulin, neutral protamine Hagedorn insulin, or premixed insulin without any allergic reactions. Four months later, PTCA was performed because of an acute myocardial infarction. The patient was administered 50 mg of protamine after active abdominal bleeding due to a right external iliac artery rupture. Three months later, recurrent raised, pruritic erythema occurred at the insulin injection site immediately after injection. Four weeks later, he experienced an attack of generalized urticaria at multiple previous injection sites (abdomen, upper arms, thighs) after injecting premixed insulin. It was accompanied by dizziness and palpitations. During the following 3 months, the symptoms recurred 3 times; one time, the patient reported losing consciousness for 2 to 3 minutes. The results of a skin

prick test found that he was allergic to human recombinant insulin and insulin lispro. The allergy was resolved by changing his treatment regimen from insulin to oral hypoglycemic agents. A Naranjo score of 10 suggested a definite relationship (score  $\geq 9$ ) between the adverse drug reaction and the insulin administration.

**Conclusions:** We present a definite case of allergy associated with insulin and insulin lispro administration. The patient had not experienced anaphylactic reactions prior to PTCA and protamine administration. (*Clin Ther.* 2009;31:569–574) © 2009 Excerpta Medica Inc.

**Key words:** insulin, hypersensitivity, allergy, anaphylaxis, PTCA, protamine.

## INTRODUCTION

Since the introduction of highly purified human recombinant insulin, insulin allergies have become less common, encountered in <1% of patients.<sup>1</sup> Different treatments such as continuous subcutaneous insulin injection (CSII),<sup>2,3</sup> administration of insulin analogue,<sup>4–6</sup> and desensitization<sup>7</sup> have been reported.

We report the case of a patient who became allergic to several kinds of insulins and insulin lispro, a human insulin analogue, after undergoing percutaneous transluminal coronary angioplasty (PTCA) and being administered protamine.

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## CASE SUMMARY

A 63-year-old Chinese man (height, 172 cm; weight, 68.5 kg) with a 17-year history of type 2 diabetes and hypertension was first admitted to the West China Hospital, Sichuan University, Sichuan, People's Republic of China, in October 2005, for uncontrolled type 2 diabetes. He administered oral hypoglycemic agents (metformin 500 mg BID; glimepiride 2 mg QD; and acarbose 50 mg TID) to control his blood glucose, and felodipine (5 mg BID) and metoprolol (25 mg BID) to control blood pressure. His fasting blood glucose (FBG) level was 7 to 8 mmol/L, and his 2-hour postprandial blood glucose (PBG2h) was 10 to 13 mmol/L. Glycosylated hemoglobin (HbA<sub>1c</sub>) was 7.8%. He had no history of smoking or allergic reactions to other drugs. Physical examination was unremarkable. Insulin treatment was initiated: 10 U intermediate insulin at bedtime (Gansulin, neutral protamine Hagedorn [NPH] [Dongbao Enterprise Group Co., Ltd., Shanghai, People's Republic of China]) and regular human insulin (Gansulin R, Dongbao Enterprise Group Co., Ltd.) before each meal: 30 minutes prior to breakfast, 20 U; lunch, 16 U; dinner, 14 U. His FBG was <6.5 mmol/L and his PBG2h was <10 mmol/L. During hospitalization, eosinophilia were  $0.37 \times 10^9/L$  (normal range,  $0.02\text{--}0.50 \times 10^9/L$ ) at admission (Table I). No local reaction was observed. After being discharged, he continued a regimen of subcutaneously

injected premixed insulin (Novolin Mix 50, Novo Nordisk Pharma Ltd., Bagsværd, Denmark) 28 U before breakfast and 16 U before dinner. The patient monitored his blood glucose regularly from then on. FBG was 5 to 7 mmol/L and PBG2h 8 to 10 mmol/L. His body weight increased ~1.5 kg from the initiation of injected insulin.

Three months later, he was hospitalized in the cardiovascular department of our hospital because of acute anteroseptal myocardial infarction. Eosinophilia were  $0.35 \times 10^9/L$ . Clopidogrel (75 mg QD), aspirin (100 mg QD), losartan (50 mg QD), amlodipine (5 mg QD), and atorvastatin (10 mg QD) were administered. He underwent PTCA with coronary stent implantation. One and a half hours later, he experienced hemorrhage shock with a blood pressure (BP) of 56/25 mm Hg due to active bleeding in his right lower abdomen. In addition to a rapid-volume infusion that included red blood cells, 50 mg of protamine was injected intravenously with 20 mL of saline to reverse the effects of heparin. An exploratory operation of his right femoral and external iliac arteries was performed immediately. Rupture of his right external iliac artery was found and repaired. Just before the PTCA, the patient had been injecting premixed insulin 32 U before breakfast and 22 U before dinner. Following surgery, the patient administered NPH insulin at bedtime ( $\leq 18$  U) and regular insulin before each meal ( $\leq 22$  U). Five weeks

Table I. Timeline of significant events.

|                   |                                                                                                                                                                                                                                     |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1990              | Type 2 diabetes mellitus was diagnosed.                                                                                                                                                                                             |
| October 20, 2005  | Insulin treatment (neutral protamine Hagedorn [NPH] at bedtime and regular human insulin before each meal) was initiated. Eosinophilia, $0.37 \times 10^9/L$ .*                                                                     |
| November 1, 2005  | Premixed insulin was administered instead of NPH insulin and regular human insulin.                                                                                                                                                 |
| January 28, 2006  | Patient was hospitalized due to acute anteroseptal myocardial infarction. Eosinophilia, $0.35 \times 10^9/L$ .                                                                                                                      |
| February 28, 2006 | Patient underwent percutaneous transluminal coronary angioplasty with coronary stent implantation. Hemorrhage shock occurred after one and a half hours. Protamine was injected intravenously. Eosinophilia, $0.35 \times 10^9/L$ . |
| March 1, 2006     | Exploratory operation of right femoral and external iliac arteries performed.                                                                                                                                                       |
| April 6, 2006     | Eosinophilia, $0.95 \times 10^9/L$ .                                                                                                                                                                                                |
| April 24, 2006    | Eosinophilia, $1.31 \times 10^9/L$ .                                                                                                                                                                                                |

\*Eosinophilia normal range, 0.02 to  $0.50 \times 10^9/L$ .

after PTCA, blood eosinophilia were observed to have increased to  $0.95 \times 10^9/\text{L}$ . At discharge, eosinophilia were  $1.31 \times 10^9/\text{L}$ .

Following discharge, his routine was to inject premixed insulin (28 U) before breakfast and regular insulin (8 U) before dinner. Three months after PTCA, raised pruritic erythema appeared at the insulin injection site immediately after injecting 28 U of premixed insulin. The erythema lasted ~30 minutes. Afterward, similar symptoms recurred each time after self-injection of premixed insulin (28 U) or regular insulin (8 U), even though the injection sites had been changed to his upper arms and thighs. Four weeks later, within 5 minutes of injecting the premixed insulin, he experienced an attack of generalized urticaria at multiple previous insulin injection sites (abdomen, upper arms, thighs). It was accompanied by dizziness and palpitations. He administered chlorpheniramine (4 mg) and the urticaria resolved after 30 minutes. During the following 3 months, these symptoms recurred 3 times; one time he lost consciousness for 2 to 3 minutes. He was rehospitalized for suspected insulin anaphylaxis.

Physical examination included the following: temperature,  $36.5^\circ\text{C}$ ; heart rate, 80 beats/min; respiration, 20 breaths/min; BP, 130/80 mm Hg; height, 170 cm; and weight, 67 kg. No rash was found on his skin. He had no diabetic retinopathy on funduscopic examination. Chest radiograph examination, abdominal B-ultrasound, and electrocardiogram were normal.

Laboratory findings were as follows: red blood cells,  $4.94 \times 10^{12}/\text{L}$ ; hemoglobin, 140 g/L; and white blood cells,  $8.35 \times 10^9/\text{L}$  (eosinophilia,  $1.23 \times 10^9/\text{L}$ ). Urinalysis for glucose, protein, and ketones were negative. Liver function, lipid profiles, serum uric acid, and renal function were normal ( $\text{HbA}_{1c}$ , 7.0%). Serum insulin autoantibody (IAA) measured by radioimmunoassay (RIA kit, Cis-Bio International, Gif-sur-Yvette, France) was 46.75% (normal range: <5%). Islet cell antibody and glutamate decarboxylase antibody measured by enzyme-linked immunosorbent assay (Biomerica, Inc., Newport Beach, California) were negative. Immunoglobulin (Ig) levels were normal: IgM, 512.00 mg/L; IgG, 13.6 g/L; IgA, 1940.00 mg/L; and IgE, 40.11 IU/L.

NPH and protamine in the premixed regimen were highly suspected as the cause of the allergic reaction. Therefore, regular insulin (Humulin R, Eli Lilly and Company, Indianapolis, Indiana) was initially chosen to control his blood glucose. However, a  $6 \times 4\text{-cm}$  firm, itchy, and nontender erythema at the injection site occurred just after administering 8 U of Humulin R and persisted for 20 minutes (Figure 1A). Thereafter, Humulin R was replaced with the human insulin analogue, insulin lispro (Humalog, Eli Lilly and Company). We observed a  $1.0 \times 0.8\text{-cm}$  induration emerge immediately at the injection site that lasted for 10 minutes (Figure 1B). The patient was then initiated on CSII using an insulin pump (Paradigm 712, Medtronic

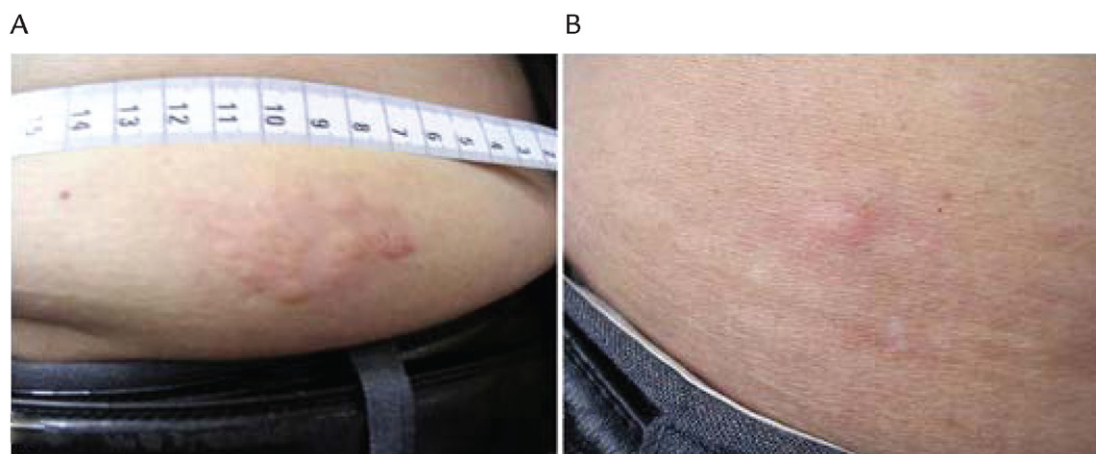


Figure 1. (A) A  $6 \times 4\text{-cm}$  firm and nontender erythema that occurred immediately at the site of subcutaneous injection of 8 U regular insulin (Humulin R, Eli Lilly and Company, Indianapolis, Indiana). (B) A local wheal with a diameter of 1 cm emerged immediately after 8 U insulin lispro (Humalog, Eli Lilly and Company) injection.

Minimed Inc., Northridge, California). Scattered, pruritic erythema occurred around the catheter implantation site on the following day.

With the patient's written consent, intradermal skin tests<sup>8</sup> were performed with several human recombinant insulins and insulin lispro. No institutional review board approval was sought. The patient was tested for allergic response to the needles alone with and without skin sterilization (70% alcohol). No local reactions occurred. Saline solution was used as negative control because the patient did not have a reaction to saline infusion. The intradermal tests with Humulin regular insulin (R), Novolin R, and Gansulin R resulted in an immediate wheal-and-flare reaction (diameters: 0.7 mm, 0.7 mm, and 0.8 mm, respectively), which resolved after 1 hour (Figure 2). Slight redness (diameter, 0.7 mm) around the bleb was noted at the insulin lispro site. A white bleb without redness and enlargement appeared at the saline site. Consequently, all insulin treatment was stopped and oral hypoglycemic agents (metformin 250 mg TID; glimepiride 2 mg QD; and pioglitazone 15 mg QD) were reintroduced in association with a low-calorie diet. One month after insulin cessation, FBG was 5 to

6 mmol/L and PBG2h was 8 to 10 mmol/L. No local or generalized reactions occurred.

The Naranjo score was 10 (Table II),<sup>9</sup> suggesting a definite probability of the allergy associated with insulin use.

## DISCUSSION

Here we report the case of a patient with type 2 diabetes who presented with local and general anaphylactic reactions to premixed and regular insulins. The intradermal skin tests were positive for human insulin and insulin lispro. Stopping insulin treatment and administering oral hypoglycemic agents were successful.

Insulin injected into the subcutaneous tissue may elicit various reactions from the immune system. Our patient presented a local wheal-and-flare reaction at insulin injection sites, with induration and pruritus that appeared just after administration and lasted for half an hour, followed by a systemic reaction. These manifestations were consistent with immediate type I allergic reactions.<sup>10</sup> Intradermal skin tests with regular recombinant human insulin and insulin lispro revealed local hypersensitive reactions. The local and systemic reactions were not observed after insu-

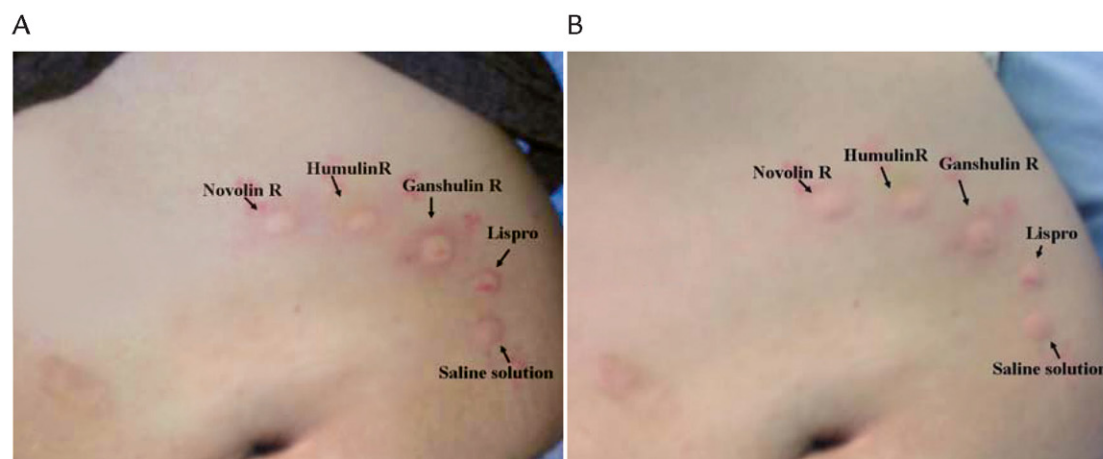


Figure 2. Intradermal skin tests with different human recombinant insulins and insulin lispro conducted in a patient experiencing an allergic reaction to insulin. (A) Five minutes after injection, immediate wheal and flare were observed at the Humulin (Eli Lilly and Company, Indianapolis, Indiana), Novolin (Novo Nordisk Pharma Ltd., Bagsværd, Denmark), and Gansulin (Dongbao Enterprise Group Co., Ltd., Shanghai, People's Republic of China) regular insulin (R) sites occurred. Slight redness around the bleb appeared at the insulin lispro (Humalog, Eli Lilly and Company) site. Only a bleb without redness and enlargement was present at the saline injection site. (B) Thirty minutes after injection, the wheals at the Humulin R, Novolin R, and Gansulin R sites were enlarged. Flare around the insulin lispro site almost disappeared without enlargement of the bleb.

Table II. Naranjo algorithm<sup>9</sup> applied to a case of allergy suspected to be associated with insulin and insulin lispro administration following percutaneous transluminal coronary angioplasty and protamine administration.

| Question                                                                                                      | Yes          | No           | Don't Know  |
|---------------------------------------------------------------------------------------------------------------|--------------|--------------|-------------|
| 1. Are there previous conclusive reports on this reaction?                                                    | +1 <u>✓</u>  | 0 <u>  </u>  | 0 <u>  </u> |
| 2. Did the adverse event appear after the suspected drug was administered?                                    | +2 <u>✓</u>  | -1 <u>  </u> | 0 <u>  </u> |
| 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 <u>✓</u>  | 0 <u>  </u>  | 0 <u>  </u> |
| 4. Did the adverse reaction appear when the drug was readministered?                                          | +2 <u>✓</u>  | -1 <u>  </u> | 0 <u>  </u> |
| 5. Are there alternative causes (other than drug) that could on their own have caused the reaction?           | -1 <u>  </u> | +2 <u>✓</u>  | 0 <u>  </u> |
| 6. Did the reaction reappear when a placebo was given?                                                        | -1 <u>  </u> | +1 <u>✓</u>  | 0 <u>  </u> |
| 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?                  | +1 <u>  </u> | 0 <u>  </u>  | 0 <u>✓</u>  |
| 8. Was the reaction more severe when the dose was increased, or less severe when it was decreased?            | +1 <u>  </u> | 0 <u>  </u>  | 0 <u>✓</u>  |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?             | +1 <u>  </u> | 0 <u>✓</u>   | 0 <u>  </u> |
| 10. Was the adverse event confirmed by any objective evidence?                                                | +1 <u>✓</u>  | 0 <u>  </u>  | 0 <u>  </u> |
| Total score*                                                                                                  | 10           |              |             |

\*Adverse drug reaction probability score: doubtful,  $\leq 0$ ; possible, 1–4; probable, 5–8; definite,  $\geq 9$ .

lin cessation, suggesting that the patient was allergic to premixed insulin, human insulin, and insulin lispro.

Ratner et al<sup>11</sup> reported that different kinds of insulin molecules could aggregate, which might result in immunogenicity. However, the patient had been previously exposed to regular insulin, NPH insulin, and premixed insulin without any allergic reactions. High titer of serum IAA might have been the cause of immunogenicity. Grammer et al<sup>12</sup> demonstrated IgE and IgG specificity against human (recombinant DNA) insulin in serum samples of a patient with human insulin allergy. The systemic symptoms experienced by their patient after premixed insulin injection were not consistent but were potentially life threatening. The authors suggested that the systemic reactions to insulin were mediated by IgE directed against the insulin molecule. The insulin-IgE complex stimulated the release that induced the type I generalized allergic reactions.<sup>13</sup> Although insulin-specific IgE antibody was not assessed in our case, it was assumed that his generalized and local allergic reactions to insulin and insulin analogue might have been type/immediate hypersensitivity-mediated by IgE IAA.

Despite determining what was causing the allergic reaction, we still did not know why the patient experienced an allergic reaction to insulins after using them for 7 months. We suspect he was immunologically sensitized by administering protamine after PTCA. Reports have found that diabetic patients may be sensitized by protamine contained in NPH or premixed insulin, resulting in allergic reactions following exposure to protamine during or after cardiac catheterization.<sup>14,15</sup> Vincent et al<sup>16</sup> reported the case of an NPH insulin-exposed patient with diabetes with immunological sensitization associated with protamine administration during cardiac catheterization. There is still debate as to whether using protamine to reverse heparin during cardiac surgery or catheterization in NPH-insulin-dependent patients with diabetes increases the risk of allergic reaction to NPH insulin injection.<sup>16–18</sup> We believe clinicians should be aware of the potential for protamine sensitization to NPH insulin in patients with diabetes.

Although the patient still had some local symptoms after using the insulin pump, methods such as CSII,<sup>2,3</sup> administration of insulin analogues,<sup>4–6</sup> and desensitization<sup>7</sup> have been reported to treat insulin allergy suc-

cessfully. However, we chose to administer oral anti-hyperglycemic drugs instead of insulin because of the insulin allergy and high titration of IAA. Following the change in treatment regimen, the patient's blood glucose was well controlled with the exception of occasional hypoglycemia occurring before meals that might be caused by the high titer of serum IAA.

## CONCLUSIONS

We present a definite case of allergy associated with insulin and insulin lispro administration. The patient had not experienced anaphylactic reactions prior to PTCA and protamine administration. The allergy was resolved by changing his treatment regimen from insulin to oral hypoglycemic agents.

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Drs. Wang and Ding contributed equally to this manuscript.

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