

Same-patient allergy to ampicillin and human insulin

C. Caruso, C. Alonzi, F. Gaeta, M. Viola, A. Romano*

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Both penicillin and insulins may cause immediate reactions, which are usually induced by an immunoglobulin (Ig) E-mediated pathogenic mechanism, occur within the first hour after the last drug administration and are manifested as urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis (1–3). The prevalence of hypersensitivity reactions to insulins has decreased because recombinant human insulin became available: serious reactions from urticaria to anaphylactic shock occur in <1% of diabetic patients treated with insulin, while local reactions occur in 15–55% of them (2, 4).

Although anaphylactic shock from ampicillin and urticaria from human insulin have been described (1, 2), to our knowledge, IgE-mediated hypersensitivity reactions by the same subject to both ampicillin and human insulin have never been reported.

We present the case of a 65-year-old woman who had suffered an anaphylactic shock (generalized urticaria-angioedema, dyspnoea, abdominal pain and hypotension) 10 min after the first dose of 1 g of intramuscular ampicillin (Amplital; Pfizer, Latina, Italy) for preoperative prophylaxis. After treatment with intramuscular adrenaline, as well as intravenous 6-methylprednisolone and chlorfenamine, symptoms resolved

completely in 12 h. Ten months before the anaphylactic shock from ampicillin, she had tolerated a full therapeutic course with the same drug.

Six months after the ampicillin anaphylactic shock, she experienced generalized flushing and urticaria 30 min after a subcutaneous injection of 15 IU of human insulin (Humulin R; Eli Lilly Italia, Sesto Fiorentino, Italy). The symptoms disappeared 6 h after 6-methylprednisolone and chlorfenamine intravenously. Insulin therapy had been started a month earlier, in the acute phase of a stroke, a macrovascular complication of type-2 diabetes. As the beginning pruriginous wheal and flare reactions had appeared each time at the injection sites 10 min after injections and had resolved spontaneously within 30 min.

One month after the urticarial insulin reaction, she was referred to our Allergy Unit and underwent an allergological evaluation. Skin testing with penicilloyl-polylysine (DAP®; Diater, Madrid, Spain), minor determinant mixture (DAP®: benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid),

benzylpenicillin (Pharmacia, Milan, Italy), ampicillin (Amplital; Pfizer) and amoxicillin (Amoxil; Glaxo Smith Kline, Middlesex, UK) was performed on two different days, in accordance with the diagnostic algorithm of the European Network for Drug Allergy (ENDA) for evaluating immediate reactions to β -lactams (1, 5). Different insulin preparations – human (Humulin R, Humulin I and Humalog 100 IU/ml; Eli Lilly), porcine (Insulin S, 28 IU/mg; Hoechst, Bad Soden, Germany), bovine (NPH-insulin, 40 IU/ml; Hoechst) – and protamine 0.02 mg/ml (Sigma, Taufkirchen, Germany) were used on the third day.

Skin tests and readings were performed as previously described (6); reagents were assessed first by prick tests and, in case of negative results, by intradermal tests. Positive controls for prick and intradermal tests were performed with histamine (at 10 and 1 mg/ml, respectively). As a negative control for prick and intradermal tests, normal saline was used. Prick and intradermal tests with insulins were also administered to 10 control subjects, 5 of whom had previously tolerated Humulin R.

Table 1. *In vivo* and *in vitro* tests for β -lactam reagents and different types of insulin

	Final concentration	Prick test	Intradermal test (Immediate reading)	Specific IgE
Penicilloyl-polylysine	1.07×10^{-2} mmol/l	–	+	n.p.
Minor determinant mixture	1.5 mmol/l	–	–	n.p.
Benzyl-penicillin	10,000 IU/ml	–	–	0.42 kU/l
Phenoxymethyl-penicillin		n.p.	n.p.	0.38 kU/l
Ampicillin	20 mg/ml	–	+	<0.35 kU/l
Amoxicillin	20 mg/ml	–	+	<0.35 kU/l
Humulin R	1.0 IU/ml	–	+	
Humulin I	1.0 IU/ml	–	+	
Humalog	1.0 IU/ml	–	+	
Human insulin (UniCAP)		n.p.	n.p.	0.56 kU/l
Porcine insulin	2.8 IU/mg	–	–	0.38 kU/l
Bovine insulin	4.0 IU/ml	–	–	<0.35 kU/l
Protamine	0.02 mg/ml	–	–	

n.p. = not performed

Assays (UniCAP®; Pharmacia Diagnostics AB, Milan, Italy) were performed for total IgE and specific ones for penicilloyl G, penicilloyl V, ampicilloyl and amoxicilloyl, as well as for human, porcine and bovine insulin. A positive result was defined as a value ≥ 0.35 kU/l. A blood sample was obtained when our patient was evaluated and the serum was kept at minus 20°C until assayed.

Our patient displayed immediate responses to PPL (at a concentration of 1.07×10^{-2} mmol/l, maximum wheal diameter of 7 mm) and to ampicillin and amoxicillin (at a concentration of 1 mg/ml in normal saline, maximum wheal diameter of 6 mm and 7 mm, respectively) as well as to Humulin R, Humulin I, and Humalog diluted 1–100 (maximum wheal diameter of 5 mm, 6 mm, and 6 mm, respectively) (Table 1). Total IgE were 46 kU/l. Assays in the patient's serum were positive to penicilloyl G and penicilloyl V, as well as to porcine and human insulin (Table 1). After the acute phase, our patient restarted the treatment with oral metformin.

Allergological tests demonstrate that our patient had IgE-mediated hypersensitivity reactions to both ampicillin and human insulin. The results of *in vivo* and *in vitro* tests were only partially concor-

dant; specifically, the latter did not confirm skin-test positivity to ampicillin and amoxicillin. However, this can be explained by the fact that *in vitro* tests are less sensitive than skin testing (1). It is difficult to establish if she also had specific IgE to porcine insulin, because of cross-reactivity or because of a coexisting sensitivity. In any case, she had never been treated with porcine insulin and human-insulin-specific and porcine-insulin-specific IgE levels were too low for inhibition studies.

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*Unità di Allergologia
Complesso Integrato Columbus
Via G. Moscati, 31
IT-00168 Rome
Italy
Tel.: +39 06 350 3782
Fax: +39 06 350 3235
E-mail: antoninoromano@h-columbus.it

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