

which was attributed to an allergic reaction to the gentamicin. Use of gentamicin was stopped and the rash resolved; however, she continued to have a fever. Ciprofloxacin and metronidazole were added. Approximately 12 hours after the fourth dose of the second induction with cytarabine, she developed hypotension with poor peripheral perfusion. She did not have other skin manifestations. She was resuscitated with 30 mL/kg of isotonic sodium chloride solution and packed red blood cells and was transferred to the pediatric intensive care unit. Ciprofloxacin, vancomycin, and meropenem therapy was continued and amphotericin was added. A complete blood cell count revealed a white blood cell count of $5.5 \times 10^3/\mu\text{L}$ with an absolute neutrophil count of $4.9 \times 10^3/\mu\text{L}$. Blood and urine cultures were negative. Computed tomography of the whole body was normal except for a small left lower lobe lung nodule. Within 24 hours, she became afebrile and normotensive. The administration of the second induction, including cytarabine, was withheld, and the treatment protocol was changed to 5 days of mitoxantrone and etoposide, which she tolerated. Two weeks later she was premedicated with hydrocortisone, 2 mg intravenously, and the cytarabine protocol was resumed with intravenous cytarabine only. Twelve hours after the second dose of the repeated second induction of cytarabine, she developed high temperatures, tachycardia, and vomiting. Use of cytarabine was stopped. She was treated with the same dose of hydrocortisone, twice daily for 4 days, after which the fever abated. She did not develop rash, hypotension, or poor perfusion. She continued to receive etoposide and daunorubicin.

Severe life-threatening anaphylactic reactions to cytarabine have been reported.⁴⁻⁶ However, at least 1 study⁷ showed the presence of circulating immune complexes in a patient with fever, rash, hypotension, and thrombocytopenia after treatment with cytarabine, supporting an immune-related delayed hypersensitivity reaction. In addition, according to Ek et al,⁸ cytarabine induces release of tumor necrosis factor α and other proinflammatory cytokines, which may directly contribute to the symptoms of the cytarabine syndrome. Therefore, desensitization was deemed inappropriate. Instead, a premedication protocol was devised. Intravenous methylprednisolone, 1 mg/kg every 6 hours, diphenhydramine, 1 mg/kg every 6 hours, and ranitidine, 1 mg/kg every 12 hours, were given for 2 days before the administration of high-dose cytarabine infused for 3 hours. This regimen was continued throughout the 5-day treatment course and for 1 day after completion. The cytarabine was tolerated without reaction. Although the reaction was not thought to be due to an IgE-mediated mechanism, both histamine₁- and histamine₂-receptor blockers were included in the protocol because of reports of life-threatening hypersensitivity reactions.⁴⁻⁶ In summary, a premedication and concurrent treatment protocol was successful in allowing the administration of cytarabine in a patient with cytarabine syndrome.

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DETEMIR INSULIN-INDUCED ANAPHYLAXIS

A 79-year-old man with diabetes mellitus of at least 10 years of evolution was referred to our outpatient clinic because of suspected insulin allergy. He had a clinical history of stroke, circulatory insufficiency, and prostate hypertrophy. Some days ago his endocrine specialist changed his previous protamine-aspart insulin treatment to detemir to achieve best metabolic control. After 2 or 3 days of treatment, he presented with sudden dyspnea, dysphagia, itching, and edema in the injection site less than 1 hour after the insulin administration. He required emergency assistance with oxygen, parenteral corticosteroid, and antihistamines. Although he did not report previous use of detemir insulin at first, administration during a former hospital stay was recorded. After consulting with his endocrine specialist, he again started taking protamine-aspart insulin, with good tolerance but poor metabolic control.

A skin prick test with full strength substances and a 1/10 dilution intradermal test were performed with several types of insulin and protamine. Skin prick test concentrations were 100 U/mL for insulins and 10 mg/mL for protamine.¹ Five nondiabetic individuals were tested to find the optimal concentration for a protamine skin test. A skin prick test with latex (ALK-Abelló, Madrid, Spain) was also performed. All results were read at 20 minutes. Histamine and saline were used as positive and negative controls, respectively.

After skin testing, subcutaneous tolerance with some types of insulin was tested under glycemic control to achieve a dose of 10 U. Results of the skin test to insulins are given in Table 1. Only glargine and glulisine insulin yielded negative intradermal test results. The results of a skin prick test with latex were negative. The results of a skin prick test with detemir insulin were positive at 100 U/mL. An intradermal test was not performed. Five healthy controls had negative detemir insulin skin prick test results. Tolerance was performed without incidence with glulisine and glargine insulin.

The patient was diagnosed as having selective allergy to detemir insulin, showing good tolerance to glargine and glulisine insulins. Desensitization was considered² but finally rejected because of the patient's age, associated morbidity, and existence of safe alternatives. After talking with his endocrine specialist, he decided to change treatment to glargine and glulisine insulin, with partial improvement in metabolic control.

Insulin allergy is a rare condition (less than 1% of patients with human insulin preparations).¹ It usually appears in a diabetic patient after a variable period of treatment. Symptoms range from local mild

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Table 1. Skin Test Results

Agent tested	Wheal/flare diameter, mm	
	SPT	ID test
Protamine	Negative	5/15
Rapid (Actrapid; Novo Nordisk, Bagsværd, Denmark)	Negative	6/17
Aspart (Novorapid; Novo Nordisk)	Negative	8/20
Lispro (Humalog; Lilly, Indianapolis, Indiana)	Negative	8/21
Glargine (Lantus; sanofi-aventis, Bridgewater, New Jersey)	Negative	Negative
NPH (Humulina NPH; Lilly)	Negative	11/29
Detemir (Levemir; Novo Nordisk)	14/40	Not performed
Glulisine (Apidra; sanofi-aventis)	Negative	Negative

Abbreviations: ID, intradermal; SPT, skin prick test.

reactions to anaphylaxis, and insulin resistance and poor glycemic control are usually present.³

Cross-reactivity between human insulin and different insulin analogues has been described but its clinical significance on skin tests is difficult to evaluate because even 40% of asymptomatic diabetic patients show positive skin test results or specific IgE to insulin.¹ In some patients, these sensitizations could play a role in insulin resistance via IgE or IgG antibodies.³ Our patient had been using protamine-aspart insulin without problems; however, a positive intradermal test result to these substances was found. Sensitization to additives such as zinc, cresol, and glycerol was ruled out because the patient showed good tolerance to glargine and glulisine insulin, which contains these substances.

Insulin analogues are created by the substitution of 1 or more amino acids in the human insulin chain to increase duration of action or to achieve a best bioavailability. Some studies report that sensitization could be more likely with insulin analogues than with human insulin itself.⁴

Detemir is a recently marketed long action insulin analog. It is created by the elimination of the threonine amino acid at the B30

position and the addition of a myristic acid residue at B29. The first case of detemir insulin reaction was described by Darmon et al in 2005.⁵ They described a man who presented with delayed local reaction to detemir insulin and good tolerance to other analogues. After that, other cases have been reported, with local immediate or delayed reactions but no systemic reactions.^{4,6}

A small number of cases of anaphylaxis to insulin have been reported, some of them with fatal outcome.⁷ Options for treatment include oral antidiabetics (when possible), substitution to a different insulin analog, use of perfusion pumps or specific desensitization,¹ and use of monoclonal antibodies (omalizumab).⁸ To our knowledge, this is the first report of selective anaphylaxis to a newly introduced detemir insulin with good tolerance to other insulin analogues.

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Erratum

In the article “Onset of effect of budesonide and formoterol administered via one pressurized metered-dose inhaler in patients with asthma previously treated with inhaled corticosteroids” by Kaiser et al (*Ann Allergy Asthma Immunol*. 2008;101:295–303), the data for patient-perceived onset of effect (OE) are presented for the overall population of patients 12 years or older in the abstract and for a subset of patients 18 years or older in the body of the manuscript. The “Methods” section of the abstract should read, “Postdose time to 15% or greater improvement in

forced expiratory volume in 1 second and patient-perceived OE (assessed in a subset of patients 18 years and older [study 1, n=553; study 2, n=405]) were evaluated.” The “Results” section of the abstract should read, “More patients receiving budesonide/formoterol vs budesonide and placebo reported feeling their study medication begin to work right away ($P \leq .017$; end of week 1 and end of treatment). Similar results ($P \leq .04$) were observed for patient satisfaction with how quickly they felt their medication begin to work.”