cytokines released during the allergic response. Specific IgE-eosinophilic inflammatory responses were the probable cause of her lesions.

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Insulin lispro, an alternative in insulin hypersensitivity

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Key words: adverse reactions; allergy; cutaneous tests; insulin; insulin analog; lispro.

• Adverse reactions to insulin have become less frequent since recombinant and semisynthetic types of human insulin have become available.

A 28-year-old woman with type I diabetes had been using human insulins with no adverse reaction for several years. At the time of her first adverse reaction, she was taking Mixtard™ 30/70, a human recombinant insulin. This patient has recently developed local reactions; pruritus, erythema, and swelling had taken place minutes after the administration of different kinds of previously tolerated human insulins. These reactions cleared up in 30 min, but 2–3 h later a painful and palpable lesion appeared, lasting for several days. The reaction did not depend on the human insulin type or the injection site. We confirmed our patient's reaction when she injected herself with Mixtard 30/70, which immediately produced the reaction previously described.

We treated our patient with lispro (Humalog™, Lilly), an analog characterized by the reversed positions of lysine 28-proline 29 on the insulin B-chain.

Insulin lispro, a new analog, was used as an alternative treatment for local cutaneous reaction to human insulin.

We performed cutaneous tests with different human insulins – Actrapid HM™, Insulatard HM™, Mixtard, Monotard HM™, and Ultratard HM™ (Novo Nordisk); Humulina NPH™, Humulina ultralente™, and lispro Humalog™ (Lilly) – as well as various commonly used additives (protamine, phenol, cresol, zinc). For prick tests, additives and insulins were used at commercial concentration, and for intradermal tests, at a 1/100 dilution, saline solution and histamine were used as negative and positive controls. Detection of specific IgE was performed by CAP (Pharmacia) and specific IgG and IgE by ELISA, both for human insulins and lispro. A skin biopsy of a lesion was taken 4 h after the reaction with Mixtard.

Cutaneous tests for lispro and additives were negative. Intradermal tests were positive for all human insulins tested, with an immediate reaction which cleared up in a few minutes and a delayed painful lesion which lasted for hours.

Negative specific IgE and positive specific IgG were obtained for all the human insulins, including lispro. The histologic and immunofluorescence studies were negative in the biopsy. A lispro challenge test was negative, and this analog is currently being daily used by the patient with good tolerance.

Lispro is an analog identical to human insulin, except at positions B28 and B29, where the sequence of the two residues has been reversed. These amino-acid substitutions interfere with the natural association of native monomers as hexamers (1), resulting in lispro more closely imitating the physiologic response in endogenous insulin secretion after meals (2).

The hypersensitivity mechanism involved in our patient's dual reaction is not clear. Although the immediate intradermal tests suggest an IgE mechanism, this fact was not confirmed by *in vitro* methods. Clinical data and the delayed skin responses suggest that another non-IgE immunologic mechanism – humoral or cellular – may be implicated. Furthermore, the positive IgG detected for lispro and the human insulins does not explain why lispro was well tolerated by our patient or the immunologic difference between this analog and human insulins. Lispro has been a useful alternative treatment in some cases (4, 5).

There are only a few immunologic studies on lispro; in monkeys, Zwickl (3) has demonstrated that lispro had lower immunogenicity than other insulins; in man, Frigerio (6) has suggested that the reversed positions 28–29 may alter the anti-insulin antibody affinity for this epitope and that the lispro monomeric state faculty may cause a lower pathogenicity, due to an altered immunocomplex formation. Kumar (7) has obtained very high titers of *in vitro* specific IgE and IgG for lispro and human insulins, which show complete cross-reactivity. For the latter author, the main immunogenic epitopes of the insulin remained unchanged in lispro; this

analog may have a reduced immunogenicity due to its rapid dissociation in monomers, rather than to differences in binding epitopes.

Further studies will be necessary to evaluate the usefulness of lispro as a therapeutic alternative in insulin adverse reactions as well as to determine how its structure affects the human immune response.

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Acetaminophen hypersensitivity

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Key words: acetaminophen; aspirin; challenge; cross-sensitivity; hypersensitivity.

● Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin (ASA) are cyclooxygenase inhibitors which can cause intolerance in a large percentage of asthma patients (1). Acetaminophen is a well-accepted substitute for NSAIDs for such sensitive patients. Several animal models have shown that acetaminophen may also be a weak cyclooxygenase inhibitor (2), but there are only a few case reports of patients with ASA sensitivity who also had a drop in FEV_1 after challenge with acetaminophen (3, 4) and of patients with systemic sensitivity to acetaminophen (5, 6).

Four young patients with hypersensitivity to acetaminophen presented with airway, nasal, and cutaneous reactions, all of whom cross-reacted with aspirin and were atopic.

We present four acetaminophen-sensitive patients whom we treated during the past 6 years.

The patients were evaluated at the Allergy Clinic of the Tel Aviv Sourasky Medical Center (Israel), which accepts referrals from all over the country as well as from the military. All four were atopic and three were also actively asthmatic. Their mean age was 21 years (range 16–28 years), and the onset of symptoms was reported to have been approximately 1 year before this referral.

All the patients were interviewed by an allergist. Skin tests were performed with the following allergens: mite, mixed grasses, mixed weeds, mixed molds, cat, dog, cockroach mix, histamine, and saline control. Three patients were sensitive to mite in addition to other allergens, and one to grass, trees, and molds. All the patients underwent spirometry (Fukuda, spiroanalyzer) for evaluating changes in pulmonary function after challenge with the drugs.

Each patient was blindly challenged with a doubling dose of ASA, beginning with 32 mg. Spirometry was performed at baseline and every 30 min afterward until there was an obvious drop of 20% or more in FEV_1. The same procedure was then performed with acetaminophen 7–14 days later.

All four atopic patients were highly sensitive to ASA at doses ranging from 32 to 126 mg. Each responded to ASA with rhinoconjunctivitis, urticaria, and a significant drop in FEV_1 (mean 32%). These symptoms appeared from 30 to 60 min after ASA ingestion (Table 1). The results of challenge with acetaminophen are shown in Table 1: the symptoms were the same as those which appeared after ASA in each case, and the dose needed to induce symptoms ranged from 64 to 500 mg. The symptoms appeared from 30 min to 2 h after ingestion. The mean change in FEV_1 was 24%. The patients inhaled salbutamol and were injected intramuscularly with 25 mg Phenergan® to reverse the symptoms. All the patients were discharged after having been observed for 8 h, and none reported the reappearance of symptoms.

We presented four young patients with proven acetaminophen hypersensitivity documented by controlled challenge. All were highly sensitive to NSAIDs, with both ASA and acetaminophen inducing allergic symptoms in the airway and nose, and on the skin. All four patients were atopic with proven type 1 hypersensitivity to aeroallergens, and three were actively asthmatic. Three showed a significant drop in their FEV_1 when

Table 1. Response of patients to blind challenge with aspirin (ASA) and acetaminophen

	Aspirin		Acetaminophen	
Patient no.	Dose (mg) which induced symptoms	Onset of symptoms (min)	Dose (mg) which induced symptoms	Onset of symptoms (min)
1	32	30	64	30
2	64	45	250	90
3	32	20	250	90
4	126	60	500	120