

A case of urticaria induced by both hydroxyzine and cetirizine but not by levocetirizine

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Cetirizine, the carboxylated metabolite of hydroxyzine, is racemate mixture composed of equal amounts of two enantiomers, levocetirizine (R-cetirizine) and dextrocetirizine (S-cetirizine) (1, 2). Because antihistamines are the main tool for symptomatic treatment of urticaria, urticarial reaction to antihistamines may lead to errors in diagnosis and treatment. We report a case of generalized urticaria induced by both cetirizine and hydroxyzine, but not by levocetirizine enantiomer, which was confirmed by single-blind placebo-controlled challenge tests.

A 22-year-old male presented with severe aggravation of generalized urticaria. Previously, he was diagnosed as chronic idiopathic urticaria, asthma, and allergic rhinitis. He had frequently taken cetirizine and hydroxyzine without aggravation of symptoms and was taking only loratadine for recent 3 months. He was prescribed with cetirizine and montelukast 2 days ago because of aggravation of nasal and asthma symptoms. Four hours after the administration of these drugs, he presented with severe generalized urticaria. He visited the clinic and because drug allergy was suspected,

cetirizine and montelukast was stopped and the urticarial lesions disappeared spontaneously within 5 days. Blood eosinophil count was $351/\text{mm}^3$ and total IgE was 799 IU/ml. Skin prick testing with common inhalant allergens revealed strong sensitization to house dust mites and multiple pollens.

Single-blind placebo-controlled challenge tests were performed with hydroxyzine (Ucerax®; UCB Korea, Seoul, South Korea), cetirizine (both Zyrtec®; UCB Korea, and a generic drug Alled®; Il Yang Pharm, Yung-In, South Korea), levocetirizine (Xyzal®; UCB Korea), loratadine (Clarityne®; Yuhan, Seoul, South Korea), fexofenadine (Allegra®; Handok, Seoul, South Korea), ebastine (Ebastel®; Bo Ryung Pharm, Seoul, South Korea), chlorpheniramine (Pheniramin®; Yuhan), montelukast (Singulair®; MSD Korea, Seoul, South Korea), and placebo. As a result, challenge test with cetirizine, and hydroxyzine reproduced the generalized urticaria after 3 and 4 h of challenge, respectively, whereas levocetirizine and other drugs including placebo, provoked no adverse reactions (Table 1). Skin prick testing with hydroxyzine (Ucerax®; UCB Korea), cetirizine (Zyrtec®; UCB Korea) and levocetirizine (Xyzal®; UCB Korea) tablets dissolved in 0.9% saline (0.01, 0.1, 1%) and intradermal testing with the same antihistamine preparations (0.001,

0.01%) were all negative. Antihistamine-specific IgE was not detected with ELISA test, which was performed according to a method described previously (3) by conjugating human serum albumin with each of hydroxyzine, cetirizine, and levocetirizine.

Antihistamines are the cornerstone of the management of chronic urticaria and many allergic diseases and urticarial reactions to antihistamines are rare conditions. An extensive literature search resulted in only one case of levocetirizine induced urticaria (1) and four cases of cetirizine induced urticaria (2, 4–6), where only one study provided with blinded challenge tests to multiple antihistamines (6). However, they did not evaluate the response to levocetirizine enantiomer of cetirizine.

The underlying mechanism of cetirizine induced urticaria remains mainly unknown. Nonallergic hypersensitivity to cetirizine was advocated as the mechanism (2, 5). In our case, negative response to skin testing and absence of drug-specific serum IgE in ELISA test suggest that the reaction might be an nonallergic hypersensitivity, and not a type I hypersensitivity. The negative result of challenge test performed with levocetirizine is very remarkable because levocetirizine is only an enantiomer of cetirizine with same chemical structure. This result suggests that dextrocetirizine enantiomer

Challenge test with levocetirizine was negative in a patient showing urticaria to hydroxyzine and cetirizine.

Table 1. Single-blind placebo-controlled challenge tests

Drug	Dose (mg)	Family	Result
Hydroxyzine	25	Piperazine	(+)
Cetirizine (Zyrtec®)	10	Piperazine	(+)
Cetirizine (Alled®, generic drug)	10	Piperazine	(+)
Levocetirizine	5	Piperazine	(–)
Loratadine	10	Piperidine	(–)
Fexofenadine	120	Piperidine	(–)
Ebastine	10	Piperidine	(–)
Chlorpheniramine	4	Alkylamine	(–)
Montelukast	10		(–)
Placebo	–		(–)

might be the causative molecule of cetirizine induced urticaria in our case, unlike the case of levocetirizine induced urticaria previously reported (1).

To our knowledge, this is the first case in which urticaria occurred with cetirizine but not with levocetirizine enantiomer.

We suggest that cetirizine and its parent drug, hydroxyzine, should not be used if either one of these antihistamines causes urticaria. Levocetirizine, the R-enantiomer of cetirizine, could be a safe alternative after confirming its safety with challenge test.

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