

ANAPHYLAXIS DUE TO TREATMENT OF GASTRIC PROTECTION

A 36-year-old woman, a nurse with antecedents of contact allergy to nickel and nonallergic asthma, working in the hospital delivery room presented with generalized rash, pruritus in palms and soles, difficulty in breathing, and lip edema 10 minutes after taking 1 tablet of ibuprofen, 600 mg, and 1 tablet of ranitidine chlorhydrate, 300 mg. She went to the emergency department, and her symptoms were controlled with adrenaline and intravenous corticoids, with a good response. When she went to the allergist consultation, 7 months later, she remembered only the ingestion of ibuprofen but forgot to mention the ranitidine. The result of a prick test with ibuprofen was negative, and the results of oral challenge tests with paracetamol and acetylsalicylic acid were also negative. She was diagnosed as having anaphylaxis, possibly caused by ibuprofen, and told to avoid the anti-inflammatory agents of the propionic acid family.

Three years later, she took 1 tablet of ranitidine chlorhydrate, 300 mg, for dyspepsia; 5 minutes later, she presented with symptoms of anaphylaxis as in the previous episode, with improvement with treatment in the emergency department. She did not take other medicine and did not have antecedents of food allergy. She was referred to our section of allergology 1 month later.

Her hemogram showed values that were inside normal; her biochemistry and tryptase levels were also inside normal. The results of a skin prick test and oral challenge with ibuprofen, 600 mg, were negative.

The result of a skin prick test performed with ranitidine chlorhydrate, 10 mg/mL (Zantac injectable solution; GlaxoSmithKline Laboratories, Madrid, Spain) was positive, with a wheal of 12×10 mm. The wheal of a prick with histamine was 5×5 mm. The result of the same prick of ranitidine in 5 atopic and 5 nonatopic individuals was negative.

The results of skin prick tests with cimetidine, 40 mg/mL, and famotidine, 4 mg/mL, were negative. The results of intradermal tests with cimetidine, 0.4 mg/mL and 4 mg/mL, and famotidine, 0.04 mg/mL and 0.4 mg/mL, were negative. The patient refused to perform an oral challenge test with these histamine₂ (H₂)-receptor antagonists.

We sent serum samples of our patient to the reference immunology laboratory to determine the ranitidine specific IgE level because the symptoms and prick test positive result could justify an IgE-mediated reaction. Ranitidine was conjugated with bovine serum albumin, and the level was determined by the dot-blot technique and UniCAP 100 (Pharmacia Diagnostics, Uppsala, Sweden). The results were negative by quimioluminescence testing, and the level was less than 0.10 kU/L.

Cases of ranitidine allergy have been reported with different clinical manifestations, such as contact sensitivity in exposed employees of a pharmaceutical manufacturing plant¹; allergic dermatitis due to oral ranitidine²; UV-B photosensitivity, urticaria, and pruriginous rash³; rhinitis and asthma⁴; anaphylaxis⁵; and skin reactions such as erythema multiforme and toxic epidermal necrolysis. Ranitidine-induced anaphylaxis has been reported in few cases despite its frequent use in clinical practice. In the first cases, the affected individuals were obstetrics patients for the most part; later, they were patients with digestive disease.⁵

We present a case of anaphylaxis caused by ranitidine. This H₂-receptor antagonist, also used as part of the treatment of chronic

urticaria, mastocytosis, and even anaphylaxis, would be recognized by the immune system of the patient as an allergen. The clinical history and positive skin prick test result are compatible with an immediate IgE-mediated reaction, but the results of 2 methods in the reference immunology laboratory to determine specific IgE antibodies were negative in most reports. IgE sensitization has been demonstrated only in 1 previous report using an enzyme-linked immunosorbent assay method⁶; another report demonstrated leukocyte histamine release in vitro.⁷ To our knowledge, the exact pathophysiologic mechanism of the development of sensitization to ranitidine is unknown.

The results of skin tests with famotidine and cimetidine were negative, as in other investigations.⁵ The reports of cross-allergy in the H₂-receptor antagonists are few and the results are contradictory, but reports conclude that it is necessary to undergo an oral challenge test with each H₂-receptor antagonist to prove their tolerance.⁸ Our patient preferred to avoid all the H₂-receptor antagonists and instead took proton pump inhibitors.

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SERUM EOSINOPHIL-DERIVED NEUROTOXIN IN CHILDHOOD ATOPIC DERMATITIS: A USEFUL MARKER OF DISEASE ACTIVITY?

Atopic dermatitis (AD) is a chronic and recurring allergic inflammatory skin disease frequently associated with peripheral eosinophilia.¹ Eosinophils play a role in the airway inflammatory process of AD by which the activated cells release granule proteins such as eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN). Although urinary EDN concentration is reportedly related to the severity of AD,^{2–4} it is not apparent that serum EDN level is associated with the activity of AD. This study evaluates serum EDN as a useful marker of AD severity in children.

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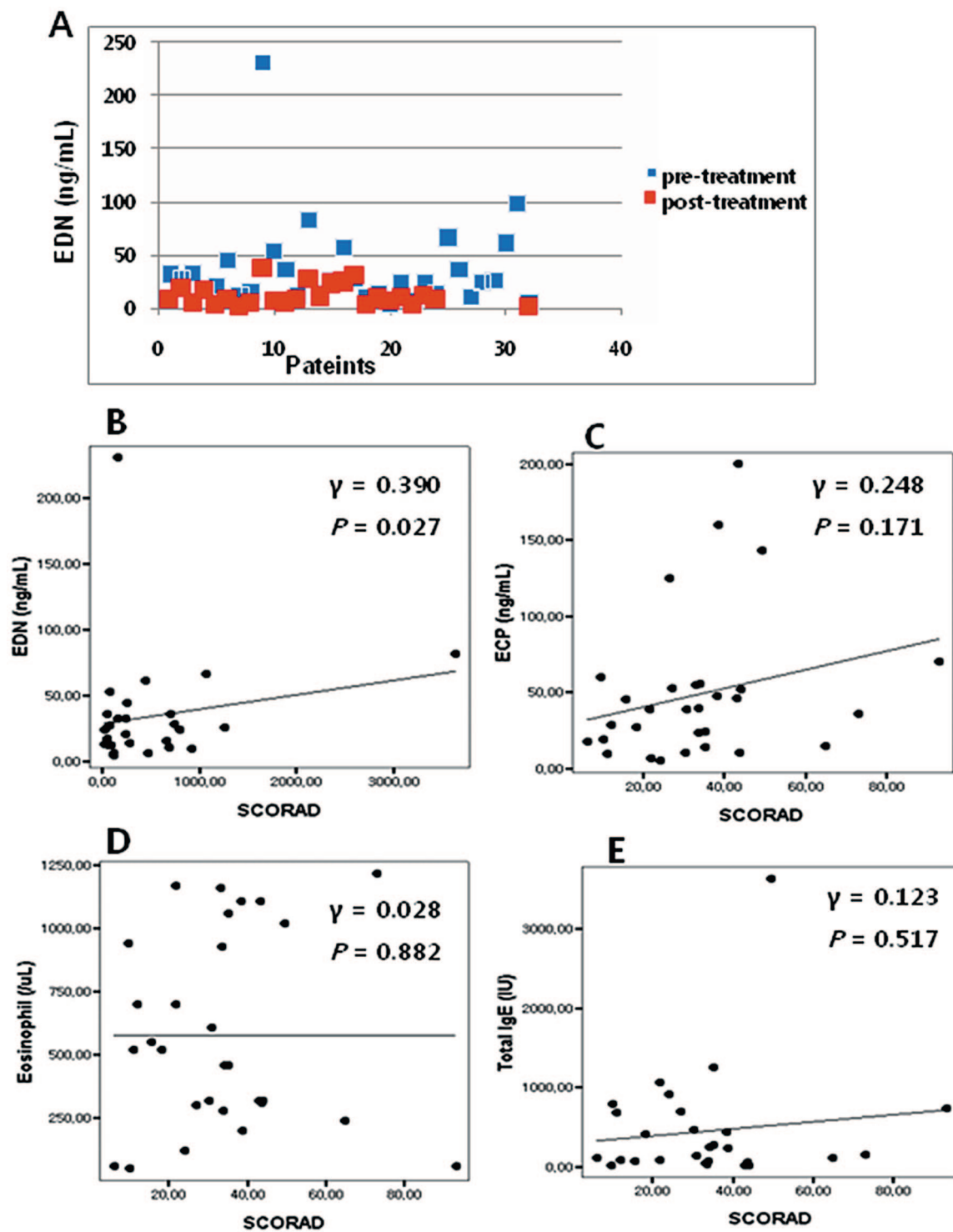


Figure 1. Correlation between the SCORing Atopic Dermatitis (SCORAD) index and other variables: serum eosinophil-derived neurotoxin (EDN) (A), eosinophil cationic protein (ECP) (C), blood eosinophils (D), and total IgE (E). Serum EDN level shows a positive correlation with the SCORAD index (B).

Thirty-two pediatric patients with mild to severe AD and 13 controls were enrolled in the study at Uijeongbu St. Mary's Hospital of The Catholic University of Korea between February 1, 2008, and September 30, 2008. The mean (SD) age of the patients was 53.16 (50.34) months (range, 3–178 months). We measured the serum EDN levels of the patients using an enzyme-linked immunosorbent assay kit (kit 7630; MBL, Nagoya, Japan) and ECP and total IgE levels using ImmunoCAP (Phadia AB, Uppsala, Sweden). After treating all the patients with conventional methods (topical corticosteroid ointments, moisturizers, and topical antibiotics in cases of skin infections), 25 patients were followed up regarding serum EDN and ECP. The clinical severity of AD was evaluated using the objective and total SCORing Atopic Dermatitis (SCORAD) index. Data are presented as mean (SD). Correlation coefficients were obtained using the Simple correlation analysis.

Blood eosinophil counts were higher in patients vs controls (5.3% [3.63%] vs 1.86% [2.22%]; $P < .01$). Mean levels of serum EDN were greater in patients vs controls (36.25 [42.18] ng/mL vs 11.23 [5.8] ng/mL; $P < .05$) and were significantly decreased in patients after treatment (36.25 [42.18] ng/mL vs 12.37 [9.79] ng/mL; $P < .01$) (Fig 1A). Patients' serum ECP levels were also decreased after treatment (48.09 [46.26] ng/mL vs 19.16 [18.96] ng/mL; $P < .01$) but were not significantly different from those of the control group before treatment (48.09 [46.26] ng/mL vs 28.51 [16.74] ng/mL; $P = .16$). Although serum EDN levels were positively correlated with blood eosinophil counts ($\gamma = 0.491$, $P = .005$), the objective SCORAD index ($\gamma = 0.356$, $P = .045$), and the total SCORAD index ($\gamma = 0.39$, $P = .03$) (Fig 1B), serum ECP levels, blood eosinophil counts, and total IgE levels were not correlated with the index (Fig 1C–E). ECP levels were positively correlated with serum total IgE levels ($\gamma = 0.41$, $P = .02$) but not serum EDN levels.

In this study, we investigated whether serum EDN levels are associated with the severity of and other variables in childhood AD. Our results correspond well with those of earlier studies noting that urinary EDN level is related to the severity of AD.^{2–4} Although urine sampling is an easy and noninvasive method in children, we speculate that serum rather than urinary EDN levels reflect the inflammatory condition of AD because it is the waste product.

On the other hand, the present findings regarding serum ECP are in contrast to the results of Pucci et al⁴ that serum ECP levels in infants and young children with AD correlate with disease severity. Although serum ECP concentration has been presumed to be associated with allergic disease activity in previous studies,^{5–7} there is a debate on its usefulness as a marker of allergic inflammation owing

to its poor consistency and diurnal variation in measurement.⁸ In addition, we believe that serum EDN reflects AD severity better than serum ECP because the serum levels of EDN, but not ECP, are statistically correlated with the SCORAD index. Although blood eosinophil counts and serum total IgE levels have been commonly used to estimate atopic inflammation, we could not demonstrate their usefulness in determining AD severity in the results.

Furthermore, we also attempted to perform the changes in serum EDN levels before and after treatment to evaluate whether they may reflect the efficiency of treatment. The levels of serum EDN and ECP were decreased in AD after treatment, suggesting that they are good variables for monitoring effectiveness. In conclusion, the serum EDN level is a useful marker for evaluating the disease activity of AD in childhood.

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