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Nizatidine anaphylaxis

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Nizatidine is a powerful specific H₂ receptor antagonist.¹ Like cimetidine, ranitidine, and famotidine, it belongs to the group of imidazole derivatives.

We therefore considered it interesting to report the case of a female patient who complained of a series of clinical signs suggesting anaphylaxis, although subsequent tolerance to other anti-H₂ drugs was good.

CASE REPORT

A 59-year-old woman, with a personal history of diabetes mellitus, gastroduodenal ulcer, and hiatal hernia experienced acute urticaria, odynophagia, laryngeal stridor, dyspnea, angioedema of the lips and tongue, dizziness, and hypotension, 30 to 40 minutes after taking the first dose of nizatidine (Distaxid, 300 mg capsules). She required urgent medical treatment and was subsequently referred to the emergency department of our hospital.

On arrival, she had a blood pressure of 160/80 mm Hg, normal lung auscultation, and clear improvement of laryngeal stridor, although a moderate residual urticaria persisted.

METHODS

The patient and 10 healthy control subjects were included in a double-blind skin prick test, which was done on the upper forearm with cimetidine (4 mg/ml), ranitidine (10 mg/ml), famotidine (10 mg/ml), and nizatidine (10 mg/ml). All skin prick test results were negative. Neither the patient nor any control subject was taking or had taken any medication that could interfere with the results of these tests.

Intradermal skin tests were performed with nizatidine at various concentrations (1:100,000, 1:50,000, 1:10,000, and 1:1000), which were obtained by diluting nizatidine in saline solution (prepared on the day of testing). A positive intradermal reaction was observed in the patient at the concentrations of 1:10,000 and 1:1000. This test result was negative in the control subjects.

After obtaining the patient's written informed consent, we performed oral challenge tests with increasing doses of anti-H₂ drugs, the excipients of the Distaxid 300 mg capsule (starch powder, free-flowing starch, povidone 90, sodium carboxymethylcellulose, free-flowing silicone, and talc) and with the capsule emptied of the preparation, until the therapeutic dose was reached, according to a single-blind method. The doses were

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increased at hourly intervals, with at least 24 hours between each challenge. Finally, the challenge with nizatidine was performed at a dose of 20 mg.

RESULTS

Results of the oral challenge tests with therapeutic doses of cimetidine, ranitidine, famotidine, excipients of the Distaxid capsule, and the empty capsule were negative. However, 15 minutes after the administration of 20 mg of nizatidine, the patient suddenly experienced laryngeal oppression, dysphonia, dysphagia, dry mouth, moderate flushing, and generalized skin pruritus; no hypotension or bronchospasm was observed at any time. The symptoms disappeared after the injection of epinephrine (0.1% solution) and 12 mg of intramuscular betamethasone.

The guidelines contained in the Declaration of Helsinki of the World Medical Association were followed at all times.

DISCUSSION

Among the side effects frequently caused by H_2 -receptor antagonists, the following have been recorded: a range of skin symptoms (e.g., sweating, urticaria and/or angioedema, rash, vasculitis, contact dermatitis, and exfoliative dermatitis), as well as fever, eosinophilia, diarrhea, dizziness, and mental confusion. Laryngeal edema, bronchospasm, hepatitis, nephritis, encephalitis, myopathy, anaphylactoid reactions,²⁻⁴ and systemic anaphylaxis are much rarer.⁵

The immediate clinical symptoms presented by this patient, her positive skin test results, and the negative test results in the control subjects, with the positive oral challenge test result, indicate that nizatidine is the cause of the clinical symptoms and suggest the existence of an IgE-mediated mechanism.

On reviewing the literature, we did not find any case similar to ours.

The ability of H_2 antagonists to increase serum histamine by displacing it from its receptors is well known, particularly after a rapid intravenous infusion. It has been postulated that a similar event may occur after oral administration of these drugs, which would account for the appearance of anaphylactoid symptoms on some occasions.

In our case, it is likely that this drug-induced mechanism does not form part of the symptoms because after administration of other compounds with the same activity on H_2 receptors, no positive response was obtained.

In short, in our patient we have demonstrated that the drug involved in the symptoms described above is nizatidine and that the causative mechanisms could be mediated by IgE. It does not seem to be attributable to a drug-induced mechanism, and there is no cross-reactivity with ranitidine, cimetidine, or famotidine. We were unable to prove the existence of a cross-reactivity with nitrofurantoin because the patient refused to continue with the oral challenge tests. It is also worth pointing out that the appearance of the clinical symptoms after the first dose of the drug is rare. This is difficult to account for, unless the patient had unknowingly received a previous dose of the drug.

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