alcohol as a coloring agent, and in IUDs. It is also used as a pesticide and a fertilizer.

Its sensitizing capacity is extremely low: in addition to external professional exposure (8), internal exposure to copper sulfate, with the appearance of systemic contact dermatitis, has become increasingly significant. Hocher et al. (9) reported a case of interstitial nephritis due to a copper-containing IUD.

Zabel et al. (4) and Hausen & Hohlbaum (10) performed allergologic examinations on several women who exhibited different degrees of cutaneous complaints after wearing a IUD, and who had a low incidence of positivity to the copper sulfate patch test; in all women, removal of the IUD caused remission of the symptoms.

Systemic contact dermatitis is an allergic disease that can be caused by various immunoreactions; however, T-cell-mediated reactions are involved (11). In experimental animals (12), it has been shown, with a radioactively labeled copper IUD, that small amounts of the metal are absorbed through the mucous membrane and carried to the cutis via the blood or lymph; in the cutis, the allergen is intercepted from antigen-presenting cells and recognized by T cells which migrate to the lymph nodes with blastic transformation, proliferation of cytotoxic lymphocytes, and production of cytokines. These are able to recall neutrophils and eosinophils to the reaction site and cause capillary dilation and increased permeability, resulting in a cutaneous allergic inflammation which may be responsible for the urticaria/angioedema features.

In conclusion, although there is a relatively low incidence of cases reported in the literature describing allergy to copper sulfate, it is advisable to bear the possibility of this disorder in mind, especially in fertile young women wearing a copper-containing IUD.

Key words: copper sulfate; intrauterine contraceptive device; systemic contact dermatitis.

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Cutaneous delayed reaction to ranitidine

Ranitidine is a histamine H_2-receptor antagonist used in the therapy of gastric and duodenal ulcers, gastroesophageal reflux, and hypersecretory states. Chemically, it is a furan derivative with a molecular weight of 350.9 Da. Ranitidine is a well-tolerated drug. Many patients have been treated, and much experience has been accumulated on the safety of this drug. Headaches, tiredness, dizziness, and mild gastrointestinal disturbance are among the most frequent complaints (1). Hypersensitivity reactions and dermatologic effects have rarely been associated with ranitidine therapy (2–8).

We report on a patient who developed a cutaneous delayed reaction after taking ranitidine, a rare adverse reaction to this drug.

In February 1994, a 43-year-old woman was treated with ranitidine (Zantac®, Glaxo, UK) 300 mg once daily as the sole treatment for a duodenal ulcer. Forty-eight hours after starting treatment, she developed papular eruption on her arms and legs. Papules were very itchy, measured 2–5 mm, and cleared completely within 2 weeks of the drug's being withdrawn. The patient did not recall a prior exposure to ranitidine. Similar clinical reactions with the same evolution were observed in April 1994 and October 1995 after reexposure to ranitidine. The patient had neither a personal nor a family history of atopy. She gave her written, informed consent before the study.

Cutaneous sensitivity to ranitidine, other H_2-receptor antagonists (cimetidine, famotidine, and nizatidine), and a furan derivative (nitrofurantoin) was evaluated by prick and intradermal tests at 10 mg/ml, and by patch tests at 1% and 10% in petrolatum. Drugs used in test preparations were obtained as pure products from the trade-name

dealers. Phosphate-buffered saline was used as diluent for prick and intradermal tests.

Prick and intradermal tests were performed on the volar surface of the arm. Results were evaluated after 15 min, and, in addition to that, intradermal sites were examined 1, 6, 12, and 24 h later. No reaction was observed in our patient. Patch tests were carried out on the back (clinically normal skin) with Leukotest® (Beiersdorf AG, Hamburg, Germany) covered by Mefix® (Mölnlycke Health Care AB, Sweden). The patch test readings were conducted according to ICDRG guidelines at 2 and 4 days. All of them proved negative.

Lymphocyte transformation tests and histamine release tests were negative for all of these drugs.

A single-blind, controlled oral challenge was performed with ranitidine, cimetidine, famotidine, nizatidine, and nitrofurantoin. A full therapeutic dose of each drug was administered separately. The interval among oral challenges with each drug was 1 week. The patient was instructed to watch for any reaction after the administration of the drug. If there was no reaction, another drug was administered. Cimetidine, famotidine, nizatidine, and nitrofurantoin were well tolerated. Thirty-six hours after the administration of 300 mg of ranitidine, the patient noticed generalized pruritus and an eruption of papules, as described above, affecting her arms, legs, trunk, and face. Laboratory investigation, including blood cell and differential counts, erythrocyte sedimentation rate, biochemical profile, serum immunoglobulins, C3, C4, CH50, and circulating immune complexes gave normal results. A 4-mm punch biopsy of a skin lesion showed a mild dermal superficial perivascular infiltrate composed of lymphocytes. We prescribed antihistamines to be taken orally (dexchlorpheniramine 6 mg 12 h). Cutaneous pruritus and lesions resolved completely within 2 weeks after withdrawal of ranitidine.

A case of non-IgE-mediated eruption of itchy papules 48 h after starting treatment.

Ranitidine is a widely used drug, usually well tolerated. Rare cases of hypersensitivity reactions (bronchospasm, fever, rash, eosinophilia, anaphylaxis, angioedema, urticaria, etc.) have been reported (2–4). Some authors have suggested an IgE-mediated mechanism in view of the clinical findings and the positive skin prick tests with ranitidine (2, 3); others have described an anaphylactoid reaction (8) or cell-mediated hypersensitivity (4). Dermatologic effects, such as maculopapular rashes (5), allergic dermatitis (7), or toxic epidermal necrolysis (6), have rarely developed during ranitidine therapy.

We report on a patient who developed a cutaneous delayed reaction after taking ranitidine. Small papules, very itchy, appeared on the arms, legs, face, and trunk. As far as we know, only Haboubi & Asquith have reported three cases of a similar reaction associated with ranitidine. However, the latent period in our case (36–48 h) was shorter than in Haboubi & Asquith's report (2–4 weeks). These authors found deposition of C_3 and IgA in the small vessels by direct immunofluorescence. They suggested that these findings were consistent with vasculitis mediated by immune complexes (5). In our case, skin tests (prick, intradermal, and epicutaneous) all proved negative, no histologic, hematologic, biochemical, or immunologic abnormalities were found, and an oral challenge test resulted in the reappearance of symptoms. These findings, together with the clinical history, could exclude an IgE-mediated mechanism, an anaphylactoid reaction, or a lymphocyte-mediated reaction. However, the precise mechanism of the reaction remains unclear. Finally, we have not found cross-reactivity between ranitidine and other H_2-receptor antagonists (such as cimetidine, famotidine, or nizatidine) or other furan derivatives (such as nitrofurantoin). Other authors confirm our findings (2, 3, 7); only Bossi et al. have reported a case of cross-reactivity involving ranitidine, famotidine, and nizatidine (9).

Key words: adverse reaction; H_2-receptor antagonist; nitrofurantoin; ranitidine; skin; skin tests.

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