

Hypersensitivity to intravenous and oral calcitriol with successful desensitization

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CASE REPORT

A 52-year-old white woman had end-stage renal disease and had been on hemodialysis since 1988. She had a history of atopic dermatitis, asthmatic bronchitis, and sinusitis. On December 13, 1996, she underwent a subtotal parathyroidectomy for secondary hyperparathyroidism and was started on a regimen of daily oral calcitriol 0.25 µg (Localtrol, Roche) and intravenous calcitriol (Calcijex, Abbott) 1.0 µg at every dialysis treatment. Seven days later, a severe pruritic urticarial rash developed on both forearms 4 hours after an intravenous calcitriol injection; parenteral calcitriol was discontinued, oral diphenhydramine was given, and she improved. Oral calcitriol 0.25 µg every day was continued. Ten days later, generalized hives developed, and she reported difficulty in swallowing; oral calcitriol was discontinued, and the hives and swallowing difficulty disappeared. The patient had no history of allergies to any of the other medications, foods, or cosmetics she had used and denied hives or swallowing difficulties before these episodes. Because of the temporal association of her symptoms to calcitriol use and the absence of new medications or changes in her medication doses over the last several months, she was considered to be hypersensitive to calcitriol. Because she had become extremely hypocalcemic (corrected serum calcium, 6.9 mg/dL), she was admitted to hospital for intravenous calcium administration. Skin prick testing for IgE-mediated hypersensitivity was performed with the undiluted materials in the oral Rocaltrol (Roche) 0.5 µg capsules and the injectable Calcijex (Abbott) 1.0 µg/mL vials. No evidence of immediate hypersensitivity was found. Because of the patient's hypocalcemia, her apparent inability to tolerate both oral and intravenous calcitriol, and the absence of any alternative treatment, she was desensitized first to parenteral calcitriol and then to oral calcitriol after informed consent was obtained. Desensitization was performed without premedication in the intensive care unit following the protocol described by Sullivan¹ for parenteral and oral desensitization. She was desensitized first to parenteral calcitriol (starting dose, 0.00002 µg) administered by means of the intravenous route and subsequently to oral calcitriol administered by means of the oral route (starting dose, 0.0078 µg). The patient tolerated the procedures without evidence of fever, hives, urticaria, angioedema, or any symptoms suggestive of a hypersensitivity reaction. Oral calcitriol 0.25 µg daily and intravenous calcitriol 1.0 µg at every dialysis were reinstituted. Her serum calcium normalized, and she was discharged from the hospital. Since then she has tolerated both calcitriol preparations and has maintained adequate serum calcium levels, without any evidence of hypersensitivity.

DISCUSSION

To our knowledge, this is the first reported case of calcitriol hypersensitivity. We attribute the urticaria and angioedema of the throat to calcitriol administration

because it appeared to be the only likely cause, the timing was compatible, previous unpublished reports showed similar reactions, and calcitriol was the only ingredient found in both preparations. Sorbitol and food dyes red #3 and yellow #6, which are present in oral calcitriol, may cause urticaria,² but they are absent in intravenous calcitriol.

After intravenous calcitriol was discontinued, oral calcitriol was continued because of the serious risk of hypocalcemia, in the hope that the patient might have some tolerance to the oral form. Indeed, for 10 days no evidence of hypersensitivity was seen. We postulate that this temporary tolerance was induced by interaction between calcitriol and the gut-associated lymphoid system, perhaps by generation of suppressor T cells or suppressive cytokines,³ which may have persisted for some time after systemic hypersensitivity had already appeared.

As noted above, adverse reactions to calcitriol have been described previously. Erythema multiforma, swelling of the lips, and generalized hives occurring after calcitriol use are noted in the oral calcitriol package insert. The manufacturer of oral calcitriol (Roche) has case reports on record suggestive of problems similar to those experienced by our patient: a 60-year-old woman with arthritis, cancer, and hypoparathyroidism had pruritus, swelling of the tongue, and shortness of breath 5 hours after ingestion of oral calcitriol. Two other patients had periorbital edema, urticaria, and pruritus immediately after oral calcitriol administration (Roche Pharmaceuticals, personal communication). The manufacturer of parenteral calcitriol (Calcijex, Abbott) states that they have on file reports of pruritus after administration of parenteral calcitriol (Abbott Laboratories, personal communication).

We have been unable to show the presence of IgE antibodies to calcitriol by skin testing. This suggests that a non-IgE-mediated mechanism or a calcitriol metabolite may have been responsible for the adverse effect.

We have documented that rapid desensitization to calcitriol allows immediate reintroduction of the drug to treat hypoparathyroidism. Our experience suggests that desensitization to this material may be done in a safe, rapid, and effective manner, although further experience is necessary to confirm this.

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