

Skin reactions associated with bisphosphonates: A report of 3 cases and an approach to management

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Allergic reactions or skin reactions of any type or severity associated with bisphosphonates have been rarely described.¹⁻⁵ We report 3 cases of cutaneous reactions associated with bisphosphonates in 3 patients with breast cancer and outline an approach to their management.

CASE 1

A 49-year-old woman with breast cancer and skeletal metastases, taking stable doses of tamoxifen and oral morphine for 4 months, was given a single dose of pamidronate 60 mg intravenously over 4 hours on March 18, 1997. On day 4 she developed pruritus followed by hives on the dorsum of both feet and her buttocks lasting 2 hours. Prick and intradermal skin testing were conducted July 30, 1997 with pamidronate 0.03, 0.3, and 3 mg/mL concentrations. All of the skin test responses were negative; an irritant reaction at the highest dose of pamidronate was confirmed in 2 control subjects. The patient was successfully challenged with a single dose of oral alendronate (10 mg), a structurally similar oral bisphosphonate (Fig 1). On October 7, 1997, she was given a challenge with intravenous pamidronate with 1/10 of the normal dose (6 mg) set to run over the first hour. After 30 minutes, the infusion was terminated prematurely when the patient experienced generalized itching and a hive on her chin. She was given diphenhydramine intravenously, and her pruritus and hives resolved. On October 26, 1997, oral clodronate was administered without an untoward reaction. She continues to take oral clodronate.

CASE 2

A 51-year-old woman with breast cancer had been taking a stable dose of tamoxifen for 2 years. In early 1997 she was found to have skeletal metastases and started on pamidronate therapy. In April and May 1997 she received her first 2 doses of pamidronate 60 mg infused over 4 hours on each occasion. On June 20, 1997, she received her third infusion of pamidronate, 90 mg over 4 hours. Eight hours after completion of the infusion, she awoke itching and noticed generalized hives, which continued for 2 days. She had

noticed no associated swelling or difficulty breathing or swallowing. On July 17, 1997, she received her fourth infusion of pamidronate 90 mg over 4 hours. Again 8 to 12 hours after completion of the infusion, she experienced pruritus and hives without any associated breathing difficulties, which lasted 2 days. Prick and intradermal skin testing was performed with pamidronate 0.03, 0.3, and 3 mg/mL concentrations, and skin test responses were negative, except for an irritant reaction at the 3 mg/mL intradermal pamidronate site. On the same day the patient was given and tolerated a 10-mg oral dose of alendronate. She has not received any further therapy with bisphosphonates.

CASE 3

A 40-year-old woman initially diagnosed with breast cancer in 1991 presented with liver metastases and hypercalcemia in November 1997. At this time she received intravenous pamidronate 60 mg over 4 hours for treatment of hypercalcemia. On December 18, 1997, she was given an infusion of clodronate 300 mg intravenously over 2 hours. Two hours after the infusion had finished, she experienced pruritus, generalized hives, and tightness in her chest. She was given 1 dose of diphenhydramine, which she continued to take for pruritus for 1 week. The hives resolved in 1 day. Prick and intradermal skin testing to pamidronate and clodronate 0.03, 0.3, and 3 mg/mL concentrations were performed January 9, 1998. This was done earlier than usually recommended (minimum of 6 to 8 weeks after reaction) because of the therapeutic need for bisphosphonates in this patient. Skin test results were negative except for irritation at the highest intradermal concentration (3 mg/mL) of both clodronate and pamidronate. A control subject also showed a similar irritant reaction at the 3 mg/mL concentration for both drugs. The patient was subsequently successfully desensitized to clodronate (Table I). She continues to receive an oral regimen of 800 mg by mouth twice daily.

DISCUSSION

Allergic and skin reactions to bisphosphonates have been estimated to occur in less than 1% of patients.¹ It is unknown whether these reactions occur more frequently in cancer patients.

The mechanism of these reactions is unknown, although it is presumed to be IgE mediated. Symptoms of IgE-mediated reactions include urticaria, angioedema, hypotension, and/or tachycardia occurring within 48 hours after initiation of a medication. In contrast to histamine-releasing reactions, IgE-mediated reactions would not be expected to occur on first exposure.

The second and third cases that we described had histories compatible with an immediate, IgE-mediated reaction to a bisphosphonate. Although the initial reaction

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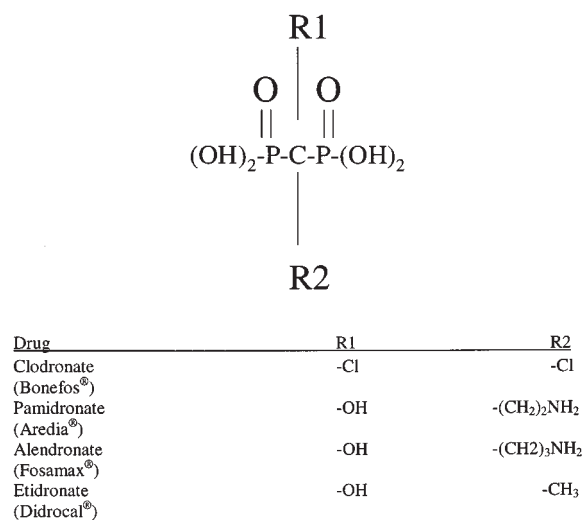


FIG 1. Structures of some commercially available bisphosphonates.

was delayed in the first case, her subsequent reaction was compatible with an IgE-mediated reaction.

Using oral challenge or desensitization, we were able to maintain 2 patients on treatment with oral clodronate after cutaneous reactions to either pamidronate or clodronate. We orally challenged the first and second patients with alendronate because it is an oral aminobisphosphonate that is structurally very similar to pamidronate. However, it did not predict subsequent reactions to pamidronate. It is possible that this is due to a histamine-releasing reaction occurring with intravenous infusion of pamidronate, an aminobisphosphonate. However, in the first case the reaction occurred on day 4, and in the second case it occurred after several uneventful administrations. This is atypical for histamine release reactions. To our knowledge, in vitro histamine-releasing studies with bisphosphonates have not been published, although aminobisphosphonates induce histidine decarboxylase, the enzyme that leads to histamine formation.⁶ In the third case we chose to continue the patient on oral clodronate because desensitization would not be maintained with intermittent infusions.

The usefulness of skin testing for bisphosphonates will require further validation. Currently, the haptens that may be involved in IgE-mediated reactions to these drugs are unknown, as is the predictive value of the parent compounds as skin-testing material. Hence, the false-negative skin test reaction rate is unknown, and therefore a negative

TABLE I. Clodronate desensitization protocol*

Dose no.	Dose	Cumulative dose
1	0.1 mg	0.1 mg
2	0.25 mg	0.35 mg
3	0.5 mg	0.85 mg
4	1 mg	1.85 mg
5	3.25 mg	5.1 mg
6	6.25 mg	11.35 mg
7	12.5 mg	23.85 mg
8	25 mg	48.85 mg
9	50 mg	98.85 mg
10	75 mg	187.85 mg
11	100 mg	287.85 mg
12	150 mg	437.85 mg
13	200 mg	637.85 mg
14	400 mg	1037.85 mg

*Each dose administered orally every 15 minutes.

skin test response does not confirm a past or predict a future IgE-mediated reaction. A positive skin test response to a nonirritant concentration (ie, less than 3 mg/mL intradermally using either pamidronate or clodronate) of a specific bisphosphonate would have suggested the formation of IgE antibody to that bisphosphonate.

Oral challenge and desensitization are useful measures to allow cancer patients to continue using this valuable class of medications. Although the cutaneous reactions are presumed to be IgE mediated, further studies are needed to determine the precise mechanism of these reactions. This will then help to guide future diagnostic tests and treatment plans.

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