

Adverse cutaneous drug reaction to alendronate

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porosis who developed maculopapular skin lesions in the head and neck region 4 months after daily alendronate intake of 10 mg (Fig. 1). Spontaneous regression occurred with some residual scaling within 6 weeks after cessation of the drug. The patient's medical history and clinical findings were otherwise unsuspicious. Histology showed a superficial perivascular spongiotic dermatitis with focal vacuolization of the basal cell layer and a mixed cellular infiltrate with few neutrophils as well as eosinophils. Comprehensive patch testing including the patient's own cosmetics were negative. 2 products (Marie Christine make up liposomal gel, Deynique anti stress refire mask) revealed doubtful positive or irritant reactions, respectively. However, subsequent repeated open application testing with both substances applied twice daily for 7 D to the flexor aspect of the forearms near the cubital fossa was negative. The minimal erythema dose for ultraviolet (UV) A and UVB was within normal limits. Sensitization to hazel, alder, and birch pollen as well as house dust mite allergens in a standard panel of prick tests was consistent with an atopic disposition. Patch testing (scratch-chamber) with alendronate 50% in water and petrolatum showed crescendo reactions at D2 and D3 (Fig. 2). Open testing (rub, prick, scratch) was negative. Control testing (closed patch tests with alendronate 50%, 10%, and 1% in water) on 10 patients without a history of bisphosphonate medication showed weak positive skin reactions (erythema with infiltration) at 50% in 3 cases, at 10% in 4 cases, and at 1% in 1 case; doubtful reactions (erythema only) were seen in 2, 0, and 1 case at these concentrations, respectively. After 2 months of complete remission oral rechallenge with alendronate in identical dosage for 3 months resulted in an isomorphic and isotopic response in our patient. All skin lesions cleared within 2 weeks after cessation of alendronate and local treatment with a steroid ointment. Substitution with risedronate (Actonel[®]) 5 mg/D was well tolerated and maintained to date without any side-effects.

Case Report

We present a 60-year-old Caucasian female with postmenopausal osteo-

Discussion

The aminobisphosphonate alendronate (Fig. 3) is a highly specific osteoclast



Fig. 1. Reddish, ill-defined, partly vesicular, itchy skin lesions at the neck.



Fig. 2. Positive patch test reactions to alendronate at D2 and D3.

inhibitor licensed for the treatment of osteoporosis in postmenopausal women. Allergy or adverse cutaneous drug reactions to bisphosphonates are scarce (1) and supposed to be immunoglobulin E (IgE) mediated (2). Aminobisphosphonates such as alendronic or pamidronic acid may additionally induce histidine decarboxylase, the enzyme forming histamine (3). Histamine-liberating effects

of bisphosphonates are unlikely because in most case reports side-effects developed several days after drug intake. However, *in vitro* histamine release tests have not been performed to the best of our knowledge. In the presented case, skin lesions developed after months of drug intake and showed a prolonged healing time after cessation of the bisphosphonate. Similarly, Roux

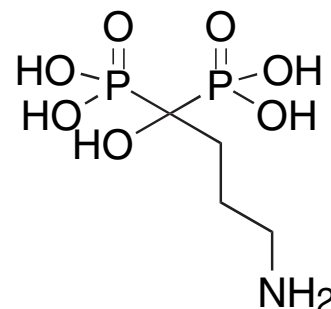


Fig. 3. Chemical structure of alendronic acid.

et al. (4) report on long-lasting skin lesions due to the non-aminobisphosphonate tiludronate. It has been speculated that skeletal retention of the compound may play a role for this phenomenon. According to the clinical and allergological data we suggest a cellular immune response to alendronate in the presented case. In view of the late onset of cutaneous inflammation in springtime after a 3-month rechallenge of the drug, we cannot exclude a pathogenetic influence of UV light. The package insert informs about the possibility of a rash with photosensitivity: rare individual cases with severe adverse cutaneous drug reactions up to toxic epidermal necrolysis have been observed.

Considering few other reports in the literature, the diagnostic value of skin testing (prick or patch) with bisphosphonates warrants further evaluation due to the obvious high rate of false negative as well as false positive results (2). For pamidronic and clodronic acid, a threshold value of 3 mg/ml has been stated for irritant reactions in intracutaneous tests: positive reactions at lower concentrations are supposed to be IgE mediated (2). As expected, our patient exhibited negative results in skin tests for immediate-type allergy while patch testing showed an infiltrated erythema at D2 supporting the suspicion of late sensitivity reactions.

Yet, taking the high rate of false positive patch test results in our control group into account a significant tendency for irritant skin reactions to alendronate is presumed. This delimits the predictive value of allergologic skin tests with bisphosphonates and calls for further studies.

The well-known aerodigestive tract mucosa irritation by alendronate and

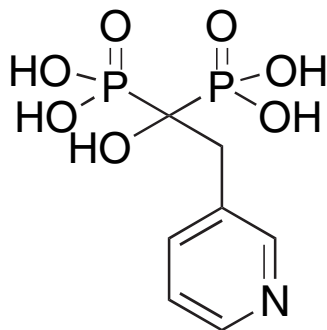


Fig. 4. Chemical structure of risedronic acid.

other bisphosphonates causing oesophagitis, laryngitis, or gastritis is thought to derive from topical effects, possibly through disruption of the cellular phospholipids barrier (5). Whether these mechanisms also influence skin testing reactivity still has to be explored.

Systemic re-exposition to the offended drug remains the gold standard for diagnosis.

Consequences for Therapy

Philipps *et al.* (2) report on 3 oncologic cases with urticarial plaques – one patient of these tolerated the change from an aminobisphosphonate (pamidronate) to a chlorinated non-aminobisphosphonate (clodronate). In another patient, a desensitization protocol for clodronate was successfully performed with 14 doses (single dose every 15 min) starting with 0.1 mg and gradually increasing up to 400 mg (1037.85 mg cumulative dose). This demonstrates that even when an immediate-type skin reaction is suspected sensitization to a specific bisphosphonate should not inevitably preclude these potent substances for the patient because different bisphosphonates with variant molecular structures may provide a safe alternative. Our patient with probable type IV sensitization to alendronate tolerated the chemically different risedronic acid (Fig. 4) well during long-term treatment.

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