Allergol Immunopathol (Madr). 2015;43(2):127–130

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Challenge test to bisphosphonates in patients with hypersensitivity reactions to drugs

Paola Lucia Minciullo[a], Alessandro Allegra[b,*], Anna D'Angelo[a], Caterina Musolino[b], Sebastiano Gangemi[a,c]

[a] *Department of Clinical and Experimental Medicine, School and Division of Allergy and Clinical Immunology, University of Messina, Messina, Italy*
[b] *Division of Haematology, University of Messina, Messina, Italy*
[c] *Institute of Biomedicine and Molecular Immunology ''A. Monroy'' (IBIM), Consiglio Nazionale delle Ricerche (CNR), Palermo, Italy*

Received 19 August 2013; accepted 23 September 2013
Available online 8 January 2014

KEYWORDS
Bisphosphonates;
Challenge test;
Drug reaction;
Safety;
Hypersensitivity reactions;
Cutaneous reactions

Abstract
Background: Bisphosphonates are a commonly used class of drugs with known efficacy in the prevention and treatment of postmenopausal and steroid-induced osteoporosis, Paget's disease of bone, hypercaelcemia of malignancy, osteolytic lesions of multiple myeloma, and bone metastases. Nitrogen-containing bisphosphonates have a favourable tolerability and safety profile, cutaneous reactions have been reported.
Methods: This is a retrospective case series study, based on the analysis of data from 1429 patients admitted to the Allergy and Clinical Immunology Division of the University of Messina between January 2011 and December 2012. Most patients had previous adverse drug reactions (ADRs) and referred to us for a challenge test with an alternative drug.
Results: We observed six patients with a past history of adverse drug reaction who needed to be tested for bisphosphonates: three patients for risedronate, two for clodronate and one for alendronate. In two years only two patients were referred to us for an adverse reaction to bisphosphonates: one to alendronate and one to risedronate. Another patient presented a previous reaction to strontium ranelate. The other three patients reported previous hypersensitivity reactions to at least two different classes of drugs. All the patients experienced no reaction using the tested drugs.
Conclusions: In our experience drug challenge tests for bisphosphonates are safe and reliable.

Introduction

Bisphosphonates (BPs) are drugs made up of two phosphonic acids joined to a carbon plus two side chains.[1]

* Corresponding author.
E-mail addresses: alessandro.allegra@tin.it, aallegra@unime.it (A. Allegra).

0301-0546/$ - see front matter © 2013 SEICAP. Published by Elsevier España, S.L.U. All rights reserved.
http://dx.doi.org/10.1016/j.aller.2013.09.010

Today, BPs are a commonly used class of drugs with known efficacy in the prevention and treatment of postmenopausal and steroid-induced osteoporosis, Paget's disease of bone, hypercaelcemia of malignancy, osteolytic lesions of multiple myeloma, and bone metastases associated with lung, prostate, breast, and other soft tissue tumours.[2]

BPs are one of the most thoroughly studied groups of drugs used. Since their first utilisation in 1969, their safety has been demonstrated through a series of trials for their various clinical uses. All approved nitrogen-containing BPs have a favourable tolerability and safety profile. After treatment with alendronate (3–10 years), risedronate (3–5 years), or ibandronate (3 years), the frequency of overall adverse events as well as withdrawal rates due to adverse events were similar between each treatment and its respective placebo arm.[3]

The adverse effects to BPs can be separated into three main groups: upper aerodigestive tract issues, effects concerning renal function, and acute-phase reactions. In 2003, a fourth adverse effect, bisphosphonate-associated osteonecrosis of the jaw, was described for the first time[4] and has been diagnosed with increasing frequency.[5–7]

However, several other heretofore unrecognised side effects of BPs were recently reported such as atrial fibrillation, hepatitis, oesophagus cancer, ocular side effects, atypical fractures of the femoral diaphysis, hypocalcaemia, and cutaneous reactions.

Hypersensitivity reactions to bisphosphonate are uncommon. Data from the European Medicines Agency report reactions to alendronate as rash, pruritus and erythema with a rate between 0.1% and 1%. Urticaria photosensitivity and angio-oedema are rare (between 0.01% and 0.1%). Severe skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis are very rare (<1 case per 10,000 users). A case of asthma and one of occupational rhinitis induced by alendronate have also been reported.[8]

Risedronate has similar rates of hypersensitivity reactions as alendronate: rash is uncommon, pruritus is rare and urticaria, angio-oedema, bullous reactions, photosensitivity and Stevens–Johnson syndrome are very rare.[8]

The intravenous BPs ibandronate and zoledronic acid can cause urticaria, angio-oedema and facial oedema – the first molecule (1–10 per 10,000) – and rash, erythema and pruritus the latter (1–10 per 1000). Both molecules can cause skin reaction at the injection site.[8] Pamidronate is reported to cause only urticaria.[9]

First generation BPs such as clodronate, tiludronate and sodium etidronate are rarely reported to cause hypersensitivity symptoms, urticaria, erythematous macular and papular rash, and asthma has been reported after clodronate use,[9] eczematous reaction after tiludronate[10] and toxic epidermal necrolysis after sodium etidronate.[11]

Our work is a case series study, based on the analysis of data from 1429 patients admitted to the Allergy and Clinical Immunology Division of the University of Messina between January 2011 and December 2012. Most patients had previous adverse drug reactions (ADRs) and were referred to us for a challenge test with an alternative drug.

We observed six patients (all females) with a past history of adverse drug reaction who needed to be tested for BPs: three patients for risedronate, two for clodronate and one for alendronate.

Case description

Case 1

A 53-year-old woman with a past history of angio-oedema after acetylsalicylic acid intake and nickel contact dermatitis, presented facial angio-oedema after the onset of treatment with alendronate for osteoporosis. The manifestation disappeared after oral corticosteroids and antihistaminic treatment.

Therefore, the patient underwent an oral challenge test to risedronate. The test was performed in two days: on the first day ¼ of a tablet was administered, the second day ½ tablet followed 3 h later, by another ½ of tablet. The test was negative and the patient started the therapy without any adverse reaction.

Case 2

A 59-year-old woman with a history of hypertension and a past history of dyspnoea after ketoprofen and clarithromycin intake, reported eyelid angio-oedema after the onset of treatment with strontium ranelate for osteoporosis. The patient performed an oral challenge test to risedronate without any adverse reaction. The test was performed in two days with the same administration schedule as case 1.

Case 3

A 59-year-old woman with a history of hypertension, dyslipidaemia, deep vein thrombosis and osteoporosis reported widespread urticaria after use of tramadol and ketoprofen. Under suggestion of her general practitioner she underwent oral challenge tests for fluconazole, paracetamol, thiocolchicoside and risedronate. Every molecule was tested in two days with the same administration schedule used in cases 1 and 2 and each test was performed at least 30 days from the other. All the tests were negative.

Case 4

A 54-year-old woman affected by type 2 diabetes, hypertension and osteopenia presented musculoskeletal pain during therapy with risedronate. Therefore, she underwent a challenge test to clodronate. The test was performed with cutaneous tests being the first day tests (skin prick test with undiluted drug and intradermal test at 1:100, 1:10 and 1:1 dilutions and undiluted) and intramuscular administration on the second day. No adverse reactions were present.

Case 5

A 77-year-old woman with osteoporosis and a past history of adverse reactions to clarithromycin and mepivacaine, under suggestion of her general practitioner, referred to our Unit

to test clodronate. She underwent intradermal injections at scalar dilutions on the first day and intramuscular injection on the second day. The test was negative.

Case 6

A 65-year-old woman affected by hypertension, dyslipidaemia, allergic rhinitis and asthma, presented a history of multidrug hypersensitivity. She reported adverse reactions characterised by urticaria, angio-oedema and oedema of the glottis after administration of several drugs such as aztreonam, cefuroxime, cyanocobalamin, rabies vaccine. She also reported urticaria during a challenge test to ciprofloxacin. Needing a treatment for osteoporosis, the patient underwent a challenge test to clodronate. The test with intradermal injections at scalar dilutions and to intramuscular injections was negative.

Discussion

It is estimated that there have been more than 190 million prescriptions in the United States for oral alendronate, risedronate, and ibandronate, and more than six million patients treated with IV bisphosphonates for cancer, worldwide (1.9 million with pamidronate, 1.2 million with zoledronate). When compared to many other therapies, especially in the cancer setting, the severity of adverse events related to BPs is generally mild and, thus, the benefits of treatment with BPs almost always outweigh the risks.[1] Hypersensitivity reactions to BPs are rare and few cases are reported in the literature.

In this work we report the safety profile of BPs regarding cutaneous reactions. In our experience, in two years only two patients were referred to us for an adverse reaction to BPs: one to alendronate (case 1) and one to risedronate (case 4); this last case did not present a hypersensitivity type reaction. Another patient presented a previous reaction to another class of drugs for osteoporosis: strontium ranelate (case 2). The other three patients reported previous hypersensitivity reactions to at least two different classes of drugs (cases 3, 5 and 6). These cases show the tendency of physicians, general practitioners in particular, to ask the patients with multidrug hypersensitivity to carry out a tolerance test to a new drug in a suitable and safe setting before using.

In our experience drug challenge tests with BPs are safe and reliable,[12] all six patients tested experienced no reaction using the tested drugs.

Conclusions

BPs are widely used in clinical practice. They are usually well tolerated with a few kinds of adverse reactions. Hypersensitivity reactions are rare and usually well managed; severe reactions are very rare and no anaphylactic shock cases have been reported.

Allergists, pharmacologists and physicians who prescribe BPs have to take in account that hypersensitivity reactions to BPs may occur, however, the reactions are usually mild and challenge tests to these drugs are safe and reliable.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Conflict of interest

All authors disclose any financial and personal relationship with other people or organisations that could inappropriately influence their work. There is no financial support which may pose a conflict of interest.

References

1. Van den Wyngaert T, Huizing MT, Vermorken JB. Disambiguating the bisphosphonates. Ann Oncol. 2008;19:1357–9.
2. Van Poznak CH. The use of bisphosphonates in patients with breast cancer. Cancer Control. 2002;9:480–9.
3. Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19:1241–9.
4. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of jaws: a growing epidemic. J Oral Maxillofac Surg. 2003;61:1115–7.
5. Alonci A, Allegra A, Bellomo G, Quartarone E, Oteri G, Nastro E, et al. Patients with bisphosphonate-associated osteonecrosis of the jaw have unmodified levels of soluble vascular endothelial growth factor receptor 1. Leuk Lymphoma. 2007;48:1852–4.
6. Allegra A, Alonci A, Penna G, Granata A, Nastro Siniscalchi E, Oteri G, et al. Bisphosphonates induce apoptosis of circulating endothelial cells in multiple myeloma patients and in subjects with bisphosphonate-induced osteonecrosis of the jaws. Acta Haematol. 2010;124:79–85.
7. Oteri G, Allegra A, Bellomo G, Alonci A, Nastro E, Penna G, et al. Reduced serum levels of interleukin 17 in patients with osteonecrosis of the jaw and in multiple myeloma subjects after bisphosphonates administration. Cytokine. 2008;43:103–4.
8. Musette P, Kaufman JM, Rizzoli R, Cacoub P, Brandi ML, Reginster JY. Cutaneousside effects of antiosteoporosis treatments. Ther Adv Musculoskelet Dis. 2011;3:31–41.

9. Phillips E, Knowles S, Weber E, Shear NH. Skin reactions associated with bisphosphonates: a report of 3 cases and an approach to management. J Allergy Clin Immunol. 1998;102:697–8.
10. Roux C, Listrat V, Villette B, Lessana-Leibowitch M, Ethgen D, Pelissier C, et al. Long-lasting dermatological lesions after tiludronate therapy. Calcif Tissue Int. 1992;50:378–80.
11. Coakley G, Isenberg DA. Toxic epidermal necrolysis, pancytopenia and adult respiratory syndrome. Br J Rheumatol. 1995;34:798.
12. Gangemi S, Guarneri C, Romeo P, Guarneri F. Safety and reliability of the drug tolerance test: our experience in 739 patients. Pharmacology. 2011;87(1–2):90–5.