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Awareness of patients receiving bisphosphonates: a cross-sectional study

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Abstract: The aim of this study was to evaluate the awareness of patients using bisphosphonates (BP) regarding their risks and benefits. Sixty-five patients using BP were included. Each participant completed a self-administered questionnaire consisting of 13 questions, including sociodemographic and general information on BP. Data were analyzed using descriptive statistics, and a binomial test was used to assess patient knowledge about BP, considering a 5% significance level. Fifty-nine (90.2%) patients were unaware or had never heard of BP drugs and only 3 (4.6%) knew their indications. Only 6 patients (9.2%) said they knew about the oral complications caused by BP. Sixty-three patients (96.9%) said they were not referred to the dentist before starting BP treatment. Patients using BP do not have satisfactory knowledge regarding the risks and benefits of BP. Physicians and dentists must be prepared to inform and counsel BP users about their adverse effects and possible risk factors. Our results emphasize the importance of public policies, whether individual or collective, to be taken to increase knowledge about BP to avoid medication-related osteonecrosis of the jaw.

Keywords: Awareness; Patient Education as Topic; Diphosphonates; Bisphosphonate-Associated Osteonecrosis of the Jaw.

Introduction

Bisphosphonates (BP) are a group of antiresorptive drugs that act by inhibiting osteoclastic activity,[1-3] used in the prevention and reduction of hypercalcemia, stabilization of bone diseases, prevention of bone fractures, and as adjuvant treatment of neoplasms with bone involvement.[4,5]

BP are organic compounds that are synthetic analogs of inorganic pyrophosphate (PPi). However, they have a central carbon atom bonded to two phosphate groups (P-C-P) instead of the oxygen atom in PPi.[6,7] This difference in structure confers resistance to chemical and enzymatic hydrolysis, so they are not converted into metabolites and are excreted unchanged by the organism.[2,7] In addition, compared to PPi, BP has a longer half-life, allowing them to affect bone metabolism by inhibiting bone resorption.[8]

Medication-related osteonecrosis of the jaw (MRONJ) is a progressive condition associated with the use of antiresorptive and antiangiogenic

therapies.[4,5] Among these drugs, denosumab and BP stand out, with BP being responsible for most cases of maxillomandibular osteonecrosis.[4,5] Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is one of the most significant adverse effects in the oral and maxillofacial area.[8-10] Thus, MRONJ includes BRONJ. By definition, BRONJ is characterized by exposed bone in the maxillofacial region that does not heal and persists for more than 8 weeks in patients who have been or are being treated with BP without prior radiotherapy in the maxillofacial region.[4,5]

In 2003, BRONJ was reported for the first time, and since then the etiopathogenic mechanism remains poorly elucidated.[4,5,8] However, dentists must be aware of this condition and know the risk factors associated with its development.[3,9,11-13] Moreover, to prevent BRONJ more effectively, the physicians who prescribe the drug should educate patients about the risks and benefits.[14] Among the few studies that evaluated patients' knowledge about the risks of oral side effects of BP use,[15-18] all showed a lack of knowledge regarding the risks and benefits of BP. None of them were conducted in Brazil.

Considering the difficulty in managing patients who use these drugs, the importance of previous dental treatment, and the clinical relevance of collateral effects, the present study aimed to evaluate the level of awareness of patients who use BP regarding risks and benefits.

Methodology

From September 2017 to June 2018, a cross-sectional study was conducted in Dental School Clinic of the School of Dentistry and in the Rheumatology ambulatory of the Clinics Hospital, both at a public university in Brazil. The study was approved by the local Institutional Review Board (protocol number 2.223.943) and complied with the Declaration of Helsinki.

A convenience sample of male and female patients being treated in the clinics of the two services was used. The patients were approached in the waiting rooms of the clinics, and informed consent was obtained from each participant. The inclusion criteria were patients older than 18 years who were using or had used BP, regardless of indication, seen at one of the two health services. The patients diagnosed with BRONJ or referred for the evaluation of oral lesions suspected of BRONJ were excluded from the study to avoid bias.

After agreeing to participate in the research, the patients were taken to an office where they were given the consent form and the questionnaire. Each participant was interviewed using a self-administered questionnaire, without the interference of the researcher. The questionnaire was adapted from previous studies,[15,16] using the current evidence on the pathogenesis and risk factors for BRONJ, and consisted of 18 questions, including sociodemographic and general information on BP and their oral complications. The form was completed in Brazilian Portuguese. After completing the questionnaire, all patients received information about oral health education and the risks and benefits of bisphosphonates, such as indications, commercial names of BP, and BRONJ prevention and management. Patients who complained of oral lesions were referred for oral examination.

The data obtained from the questionnaires were typed and analyzed in Excel (Microsoft Office) spreadsheets and tabulated in SPSS (Statistical Package for Social Sciences), version 22. Data were first analyzed by descriptive statistics, with the relative and absolute distributions of the variables. Later, the binomial test was used for the variables whose answers were yes or no to the patients' knowledge about BP, considering a 5% significance level.

Results

All invited patients agreed to participate in the study, totalizing 65 patients, and all of them responded to all the questions. Of these, 59 (90.8%) were female and 6 (9.2%) were male, with a mean age of 65.2 years (ranging from 42 to 82 years). Thirteen (20%) patients presented multiple diseases and were taking more than one BP, totalizing 78 treatments. As for indication, osteoporosis was the most common condition, observed in 59 patients (90.8%), followed by breast cancer (3 to 4.6%) and multiple myeloma

(2 to 3.1%). Arthrosis, rheumatoid arthritis, lung cancer, and osteoradionecrosis were less frequently observed (1 to 1.5% each) (Table 1).

The 78 therapies were represented by 4 distinct drugs. Alendronate was used by 57 patients (87.7%), followed by zoledronate (10–15.4%), risedronate (9 - 13.8%), and ibandronate (2–3.1%). The mean time of treatment was 39.2 months (ranging from 1 to 120 months). The meantime of oral BP therapy was 40.2 months (ranging from 1 to 120 months), whereas of intravenous BP was 32.4 months (ranging from 12 to 60 months). Of the 78 medications, 46 (58.9%) had been discontinued and 32 (41.1%) were still in used.

Table 1. Demographic data of the 65 patients.

Demographic features	n (%)
Sex	
Female	59 (90.8)
Male	6 (9.2)
Age (years)	
Mean	65.2 ± 8.2
Origin	
Dental school clinic	12 (18.5)
Rheumatology Ambulatory	53 (81.5)
Diseases	
Arthrosis	1 (1.5)
Breast cancer	3 (4.6)
Multiple myeloma	2 (3.1)
Lung cancer	1 (1.5)
Osteoporosis	59 (90.8)
Osteoradionecrosis	1 (1.5)
Rheumatoid arthritis	1 (1.5)
Bisphosphonates*	
Alendronate (O)	57 (87.7)
Ibandronate (O)	2 (3.1)
Risendronate (O)	9 (13.8)
Zoledronate (IV)	10 (15.4)
Duration (months)	
Oral	40.2 ± 27.2
Intravenous	32.4 ± 16
Treatment situation	
In treatment	32 (41.1)
Stopped	46 (58.9)

n: number of patients; O: oral; IV: intravenous. *65 patients used 78 BP medications.

Most of concomitant medications were antihypertensives (28 –43.1%), calcium (20–30.8%), and vitamin supplement (17–26.2%). Antidiabetics (6–9.2%), corticoids (4–6.2%), antiacids, synthetic hormones (2–3.1% each), antineoplastics, antidepressants, anxiolytics, antiresorptive agents (Denosumab), and peripheral vasodilators were also observed (1–1.5% each).

There were no differences in level of knowledge between oral and intravenous BP users. Most patients 59 (90.8%) were unaware or had never heard of BP ($p < 0.001$) and only 3 (4.6%) knew their indications ($p < 0.001$). When asked about oral complications caused by BP, only 6 patients (9.2%) said they knew about them ($p < 0.001$). Ulcers and osteonecrosis of the jaw (3–50% each) were the oral complications most often mentioned by these patients. Of these 6 patients, 2 (3.1%) were informed by dentists, 2 (3.1%) by physicians, and 2 (3.1%) by other means (television) (Table 2).

When questioned about trauma in the oral cavity, 13 (20%) patients underwent surgery after using BP, and 11 (16.9%) had suffered trauma from removable dental prostheses. Regarding oral care, 25 (38.5%) said they went to the dentist regularly. However, only 18 (27.7%) visited the dentist within 6 months. Of the 65 patients, 63 (96.9%) reported that they were not referred to the dentist before starting treatment with BP (Table 3).

Discussion

In this study, 90.8% of the patients did not know or had never heard of BP, and only 4.6% knew their indications, which was probably due to the fact that patients know the medications by their commercial names. However, the results revealed that there is low patient awareness. Although the physicians who prescribe the medications are responsible for providing information, studies show that professionals still know little about the indications and possible side effects of BP.[12-14,19,20] Thus, patients' unawareness of the side effects of these drugs may promote the occurrence of BRONJ, since dentists are also unprepared to evaluate

Table 2. Knowledge on bisphosphonates and oral health.

Questions	n (%)	p-value
Do you know or have you heard of Bisphosphonates?		
Yes	6 (9.2)	< 0.001*
No	59 (90.8)	
Do you know the indications of Bisphosphonates?		
Yes	3 (4.6)	< 0.001*
No	62 (95.4)	
Do you know about oral complications caused by the use of Bisphosphonates?		
Yes	6 (9.2)	< 0.001*
No	59 (90.8)	
If yes, who informed you?		
Dentist	2 (33.3)	
Physician	2 (33.3)	
Pharmacist	0 (0)	
Package insert	0 (0)	
Other	2 (33.3)	
If you know or have been informed about this subject, what are the complications caused by these drugs?		
Ulcers	3 (50)	
Muscle pain	1 (16.7)	
Toothache	2 (33.3)	
Gum disease	1 (16.7)	
Jaw necrosis	3 (50)	
Facial pain	1 (16.7)	

n: number of patients. *statistically significant.

Table 3. Oral health data of the patients.

Questions	n (%)
Did you underwent dentoalveolar surgeries after the use of Bisphosphonates?	
Yes	13 (20.0)
No	52 (80.0)
Have you ever suffered trauma (injury) caused by a prosthesis	
Yes	11 (16.9)
No	54 (83.1)
Do you visit the dentist regularly?	
Yes	25 (38.5)
No	40 (61.5)
When was the last visit?	
6 months or less ago	18 (27.7)
1 year ago	17 (26.2)
2 years ago	11 (16.9)
3 years ago	3 (4.6)
4 years ago	3 (4.6)
5 years or more ago	13 (20.0)
Before starting treatment with bisphosphonates, did the doctor refer you for consultation with the dentist?	
Yes	2 (3.1)
No	63 (96.9)

n: number of patients.

this risk.[13] A meticulous and detailed anamnesis is essential to identify users who are unaware of the BP drug group.

Osteoporosis was the indication for the use of BP in about 90% of the patients. The high selectivity of BP for bone tissue is due to the principle of their use in clinical practice.[2,7] Besides having antiangiogenic properties, their preferential absorption by hydroxyapatite crystals in the mineralized bone matrix promote inhibition of osteoclast and osteoblast activity and apoptosis of osteoclasts.[2,7] BPs are often used for the treatment of osteoporosis and osteopenia, malignant neoplasms with bone metastases, malignant hypercalcemia, and multiple myeloma[21-23] In addition, BP are also indicated for the treatment of Paget's disease, osteogenesis imperfecta,[8,21-24] and osteoradionecrosis in association with other drugs.[25]

Considering the number of BP users worldwide, the frequency and severity of adverse effects of BP are relatively uncommon and usually of low intensity, so the benefits provided by these drugs outweigh the possible risks.[1,6] Despite this, the risk of developing BRONJ increases considerably if preventive measures are not implemented. Thus, it is important to educate patients about the possible oral complications related to BP treatment, including informing patients on the importance of maintaining oral health and the contraindications for elective dentoalveolar surgeries.[8,10,21]

When asked about the possible adverse effects that BP can cause in the head and neck region, only 9.2% of patients said they were aware of them. The side effects of BP in the oral and maxillofacial region include ulcers, dental calculus, gingivitis, facial pain, and BRONJ.[3,10,16,22] BRONJ is a serious adverse reaction that affects the jaws. The prevalence of BRONJ ranges from 3 to 12% in patients receiving BP intravenously and less than 1% for patients in receiving the medication orally.[4,5]

Four patients obtained information about the risks of BP from professionals, 2 from physicians, and 2 from dentists. On the other hand, in a similar study, most patients obtained their knowledge about the prescribed drug from the package insert.[16] These data suggest that there is a failure in communication, a lack of interest on the part of professionals to properly care for and orient patients, or even a lack of knowledge on the part of the professionals themselves of the potential risks of these drugs. Allegations of delayed or missed diagnosis and failures to prevent and manage oral complications of antineoplastic therapy may result in legal action for both dentists and physicians. Epstein et al.,[26] showed that the two largest indemnities from lawsuits were due to errors in assessing the risk of BRONJ, with values of up to $12.5 million.

Alendronate was the most used BP by patients. The mean duration of treatment was 40 months for oral BP and 34 months for intravenous BP. Patients using intravenous BP have a higher risk for developing BRONJ than patients using oral BP. The duration of treatment is also a risk factor related to the drug. The longer the duration of use, the higher the risk of developing BRONJ.[4,5,8] Patients using oral BP have an increased risk of 0.1% to 0.21% after 48 months,[27] whereas intravenous users have a 1.3% increased risk of developing BRONJ after 36 months of use.[28] About 13% of BRONJ cases are related to the use of oral BP, pointing out that although it is less frequent, it can induce BRONJ.[28]

The increase in the frequency of reported cases associated with medication can be explained by a large number of patients using BP.[4,5,8] In the present study, among the 78 therapies used, 45 were discontinued (58.9%). The risk of developing BRONJ continues even after medication discontinuation. BP has a long half-life of up to 10 years.[1,7] Therefore, it is important to conduct a correct anamnesis, obtain an accurate medical history, and ask patients about the medications they are using or have used.

The combination of chemotherapy and corticosteroid use with BP use represent risk factors for BRONJ.[10,22] Common comorbidities such as diabetes, hypertension, and rheumatoid arthritis are also listed as risk factors.[10,11,24] In the present study, four patients used corticoids, twenty-eight had hypertension, and six had diabetes. When treating patients using BP, dentists must be able to identify the predisposing factors for BRONJ to minimize its development.

In this study, 13 patients underwent dentoalveolar surgeries and 11 had trauma from prosthesis after BP use. Exodontia represents an important risk factor for

the development of BRONJ.[4-6,21] About 60% of BRONJ are related to exodontia and 7% are associated with prosthetic trauma.[24] Oral trauma and oral surgeries are also risk factors.[8,21] Teeth should be preserved by non-surgical endodontic and periodontal treatments whenever possible. When extraction is unavoidable, it should be as less traumatic as possible and the wound margins should be coaptated to accelerate the healing process. Prophylactic antibiotics should also be administered.[8,29] In fact, oral evaluation before the onset of BP treatment is the most important strategy to avoid future exodontia.

Regarding oral health, 38.5% reported visiting the dentist regularly. However, only 27.7% had a dental appointment in the last six months or less. Patients with poor oral hygiene are at increased risk for the development of BRONJ.[3,10] Poor oral hygiene results in an accumulation of biofilm, which can lead to periodontal diseases and/or coronary destruction. About 85% of patients with BRONJ have periodontal disease and 13% have dentoalveolar abscesses.[30] Visiting the dentist regularly minimizes and/or prevents the progression of serious conditions that require more invasive treatment, such as dentoalveolar surgery. Patients using BP should be motivated to maintain good oral hygiene to avoid potential complications.

Only 2 patients (3.1%) reported that their physicians referred them to a dentist before starting BP treatment. A similar study reported that physicians did not inform patients that they needed to inform their dentists about BP therapy.[15] It is extremely important to refer the patient to a dentist for dental evaluation, removal of possible infectious foci, and detailed orientation on oral hygiene and risk factors for the development of BRONJ before treatment with BP.

The present study has several strengths, but some limitations need to be considered. First, all data collected were self-reported, which means that responses are subject to two types of bias: recall bias and social desirability bias, which is the tendency to underreport socially undesirable attitudes and behaviors. Second, most participants in this study were patients under oral BP for osteoporosis treatment. The authors recognize that the study would have had more power if a representative sample had been available for both application routes. Despite this, 15% of the participants were under treatment with intravenous BP. Moreover, although the prevalence of BRONJ is significantly higher in patients undergoing intravenous BP, BRONJ must be considered a potential side-effect in patients under alendronate therapy, most commonly observed in elderly female patients affected by osteoporosis,[31] which was the main population of this study. Thus, patients need to be aware of this risk. Third, the non-probability and convenient nature of the sample may over- or underreport the participants' actual perception and knowledge of BP, although most of them demonstrated a lack of awareness about this matter. The questionnaire used for data collection was adapted from previous studies, using the current evidence on pathogenesis and risk factors for BRONJ. Nevertheless, it was not validated. For further studies, the elaboration of scientifically validated tools is recommended.[15] As results vary around the world, further global studies involving different countries are needed to assess this problem more extensively.

Conclusions

The results of this study highlighted that BP users, regardless of route of administration, were not aware of risks and benefits of BP. A meticulous and detailed anamnesis is essential to identify users who are unaware of the BP drug group. Physicians and dentists must be prepared to inform and counsel BP users about their adverse effects and possible risk factors. The data also show the need to invest in public policies, whether individual or collective, that increase patient awareness about these drugs to prevent or minimize the probability of developing BRONJ.

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