

About the Author



Dr. Richard L. Wynn is Professor of Pharmacology at the University of Maryland Dental School. He holds a BS degree in Pharmacy and a PhD degree in Pharmacology. He chaired the Department of Pharmacology at the University of Maryland Dental School from 1980 to 1995. He is the lead author of the Drug Information Handbook for Dentistry, a co-author on many other dental drug publications, an author of over 300 refereed scientific journal articles, a consultant to the Academy of General Dentistry, a featured columnist, and a featured speaker presenting more than 500 courses in continuing dental education. One of his primary interests continues to be keeping dental professionals informed of all aspects of drug use in dental practice.

2,408 Patient Cases of Bisphosphonate-Associated Osteonecrosis of the Jaw Bone: The Most Extensive Review to Date

The report, published in the *Journal of Cancer Research and Clinical Oncology* in 2010, summarized the important clinical features of BP-associated ONJ pathology - based on every published case since 2003 (the year of first description) - in order to provide an accurate assessment of the disease. For evaluation of the presence of ONJ, they used the established definition of "exposed necrotic jawbones that are resistant to conventional therapy for more than 8 weeks, and occurring in patients taking BPs who never had radiation therapy." The results are broken down as follows:

Results of the Study

Sex Ratios, Locations and Stages

- 2,408 cases were reported from 134 published articles. In the 1,600 cases in which the gender of the patient was reported, 61% of the patients were women.
- In terms of lesion locations recorded from 1,580 cases, there were 65% with exposed bone of the mandible, 27% with exposed bone of the maxilla and 8% with exposed bone in both jaw bones.
- Information about the clinical stage was available for 572 patients. Of these patients, 66% were stage II (painful or infected necrotic bone), 16% were stage I (asymptomatic necrotic bone) and 18% were stage III (extraoral complications, extensive sequestration or pathological fracture).
- Eighty-eight of the stage III patients had their complications described. The breakdown was as follows: 28% had cutaneous fistulae, 26% had maxillary sinusitis, 20% had antral fistulae, 23% had pathological fractures of the mandible, 15% had soft tissue abscesses, 6% had oral fistulae and 1% had orbital abscess.

Primary Medical Diagnosis for BP Use and Type of BP Used

- The reasons for the bisphosphonate indication were reported in 1,780 patients.
- 89% of the 1,780 patients had a malignant condition for which the bisphosphonate was indicated as part of the treatment regimen. Multiple myeloma accounted for the majority of cases, followed by metastatic breast and prostate cancers and other neoplasms. These malignancies were observed in 43, 32, 9 and 5% of the 1,780 patients.
- 11% of the 1,780 patients were taking the BP for nonmalignant conditions. Osteoporosis was the most common nonmalignant disease for which the BP was taken, followed by Paget's disease and other rheumatological diseases. The occurrences for these conditions were 10, 0.7 and 0.6%, respectively, out of the 1,780 patients.
- Information from 1,694 patients was available on the specific BP used in the above medical conditions. 88% of those patients received intravenous BP therapy: 53% of those received zoledronic acid alone, 27% received pamidronate followed by zoledronic acid and 19% received pamidronate alone. Oral BP treatment was reported in 12% of the 1,694 patient cases, primarily oral alendronate (Fosamax) (77%), followed by ibandronate (19%) and other orals (4%).

Osteonecrosis Triggers

- The events that induced BP-associated ONJ were reported in 1,570 cases; most cases (67%) were induced by dental extractions. In 7% of the cases, ONJ was caused by a different factor, such as a dental pressure sore or a torus. No predisposing factor was found in 26% of patients.

Antibiotic Treatment of BP-Associated ONJ

- Antibiotic treatment of BP-associated ONJ was reported in 391 cases. Beta-lactam drugs were prescribed most frequently, including the following treatments: aminopenicillins (probably amoxicillin, 39% of patients); a combination of aminopenicillin with a beta-lactamase inhibitor (probably Augmentin®, 28% of patients); and penicillin VK (26% of patients). These treatments were followed by treatment with clindamycin (33% of patients) or metronidazole (13% of patients), or treatment with other drugs such as tetracyclines (11%) or fluoroquinolones (1%).

Surgical Treatments

- There were 593 descriptions of surgical treatments. Most (65%) were conservative, although 35% underwent major (aggressive) procedures such as extended sequestrectomies or segmental resection of the jawbones.

Experimental Treatments

- In 100 cases, patients underwent experimental procedures such as hyperbaric oxygen therapy (70 patients), platelet-rich plasma applications (4 patients), ozone therapy (12 patients), and laser tissue stimulation (14 patients).

Outcomes

- 984 patients were described for outcomes. A cure, which was defined as no further bone exposure, was observed in 35% of the patients. The length of follow-up was identified for only 366 patients. The mean for follow up was 10.48 months.
- Colonization of *Actinomyces* bacteria was observed in 70% of the 338 cases in which microbiological data were available. The study also found 732 reports of associated comorbidities. Chemotherapy (55%), corticotherapy (32%) and hormonotherapy (9%) were the most frequent concomitant therapies detected. Risk factors reported were diabetes mellitus, smoking, odontogenic infections, high cholesterol and anemia.

Discussion

This review identified total reported cases in the literature from January 2003 to September 2009. The review summarized the current knowledge through reports over a 6-year span. They retrieved 2,408 cases, 88% of which were associated with the treatment of a malignant condition, particularly multiple myeloma (43% of the cases). Of all the BP-associated ONJ cases, 67% were preceded by tooth extraction and only 35% of patients were cured.

A study by Woo, et al, published in 2006, used the PubMed database to retrieve cases of BP-associated ONJ. That study identified 368 cases. This present study, by Filleul et al, presents data from more than six times as many cases. Obviously, between 2006 and 2009, the incidence of ONJ dramatically increased.

Placing the Filleul report in perspective, the review had limitations because most of the data reviewed consisted of voluntary reports and retrospective analysis of case studies. They were unable to compare data describing treatments and outcomes. Also, there were a limited number of patients for whom precise follow-up data were available. Patient selection criteria were not reported in most of the studies. Even so, this review clearly highlights that the complication of ONJ in patients taking BPs is a continuing problem, especially since zoledronic acid and pamidronate have become the standard treatment for patients with breast cancer, multiple myeloma and other metastatic malignancies.

The authors state that prevention is always better than treatment and the establishment of meticulous oral hygiene and surgical procedures prior to the start of BP therapy is crucial. This review summarized the current clinical knowledge on BP-associated ONJ even though most of the studies reviewed were retrospective and uncontrolled.

Methods of the Study

The following is a breakdown of the methods and materials used for this study. The entire report can be found at Filleul O, Crompton E, Saussez S, "Bisphosphonate-induced Osteonecrosis of the Jaw: A Review of 2,400 Patient Cases," *J Cancer Res Clin Oncol*, 2010, 136:1117-24.

1. The authors conducted a PubMed-based lit search published between January 2003 (first description) and September 2009.
2. From the use of key phrases such as bisphosphonates, osteonecrosis of the jaw, jaw disease and so on, the authors identified 10,023 references.
3. These 10,023 references were manually sorted to extract all descriptions of patients meeting the diagnostic criteria proposed by Ruggiero. These criteria were (1) current or previous treatment with BPs, (2) exposed, necrotic bone in the maxillofacial region that persisted for more than 8 weeks and (3) no history of radiation therapy of the jaws. In addition, references were obtained from citations within the retrieved articles.
4. As a result, 134 articles were isolated that described 2,408 cases of BP associated ONJ. Clinically relevant data from every case was evaluated. These data were age and sex of patient, location of lesion(s), treatment regimen, the disease that prompted BP treatment, the clinical stage of ONJ at diagnosis and any factors predisposing the patient to the development of BP-associated ONJ, such as tooth extraction, hormonal therapy, chemotherapy and others.
5. The clinical stage of the disease was based on the classifications by the *American Association of Oral and Maxillofacial Surgery*. Stage I BP-associated ONJ was considered as an asymptomatic oral bone exposure. Clinically inflamed or infected bone exposures were defined as a stage II disease. Patients who had distant complications such as fistulae or maxillary sinusitis were considered stage III.
6. The authors evaluated various treatments used to control complications and distinguished between medical and surgical procedures. In addition, a further distinction was made between conservative and radical surgical procedures. Conservative surgical procedures responded to ordinary dental care described as limited procedures. Extensive sequestrectomies, marginal and segmental resections of the mandible and partial maxilloectomies were considered radical surgical procedures.
7. They also attempted to record the precise outcome of these patients and any associated comorbidities or infections of lesions with *Actinomyces* bacteria, whenever possible.
8. The study authors defined a patient as cured if complete mucosal closure was reported in the absence of ONJ symptoms during the last follow-up visit.

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