



BISPHOSPHONATE OSTEONECROSIS LITERATURE

DUKE TRIAL

Osteonecrosis of the jaw (ONJ) has recently been recognized as associated with bisphosphonate (BP) therapy, however there is little information on the natural history, treatment or prevention strategies for this condition¹. Bisphosphonates, particularly compounds containing an aliphatic chain with an amino group in the R2 position, (pamidronate, alendronate and zoledronate) are extremely effective and widely used in the treatment of breast cancer, prostate cancer, multiple myeloma and non-malignant bone disease. Although ONJ appears to develop in less than one percent of patients taking these drugs, the seriousness of the disease plus the current lack of treatment options makes this a very difficult clinical problem. This study will randomize 35 out of 70 patients to receive HBO in addition to their routine oral surgery therapy for ONJ and follow both groups over a 2-year period. The study design is an interventional, prospective, randomized trial with a 2-year follow up period. Seventy subjects meeting the inclusion criteria for ONJ will be recruited by participating physicians and randomized to receive 40 HBO treatments over a 4 week period or to continue their normal oral care. No subject, HBO treated or not, will be asked to change, initiate or discontinue any ongoing therapies they may be receiving from their primary care giver for ONJ or any other medical condition. The analysis will compare remission rates between the two groups while controlling for age, gender, race, previous local trauma or surgery, tumor type, diabetes, immunosuppression, bisphosphonate duration, indication (hypercalcemia), infection, corticosteroids, and thalidomide and dental hygiene. All subjects will be closely followed throughout the 24 month course of the study with weekly contacts by phone or email to log jaw pain level as well as to record any change in general medical condition. The 17 question Duke Health Profile will be used to measure quality of life indicators at 4 key points during the study.

Comparison(s): 1) clinical remission rate in patients receiving and not receiving HBO. 2) Bone turnover and molecular measures of osteoclast signaling in ONJ patients before and after HBO and relative to non-diseased controls (labs from non-diseased controls to be obtained from a companion study).

BISPHOSPHONATE OSTEONECROSIS LITERATURE

Today's FDA. 2008 Aug;20(8):38-41, 43-6.

Bisphosphonate-associated osteonecrosis: a clinician's reference to patient management.

Grewal VS, Fayans EP.

Bisphosphonates (BPs), as inhibitors of osteoclasts, are widely used in the management of metastatic bone disease and in the prevention of osteomalacia and osteoporosis. Recent cases of bone necrosis of the jaws have been associated with the use of bisphosphonate therapy. A case is presented of a patient with osteonecrosis of the maxilla with a history of long-term bisphosphonate therapy for metastatic breast cancer. The authors treated the patient and suggest appropriate patient management guidelines with reference to current knowledge. Although a definitive treatment for bisphosphonate-associated osteonecrosis has not yet been established, clinicians must be aware of the pharmacologic properties of several bisphosphonates currently available and their indications, susceptible risk factors in the development of osteonecrosis of the jaws, the clinical signs and symptoms, and recommendations for patient management, including prevention and early recognition. BPs, potent inhibitors of osteoclast-mediated bone resorption, were first introduced more than 20 years ago. Since then, they have been used widely in the management of bone diseases, including hypercalcemia related to malignancy, myeloma-related bone disease, Paget's disease and osteoporosis. They have also been shown to inhibit tumor cell proliferation and inhibit angiogenesis. These additional features have made BPs useful in the treatment of metastatic disease, including breast and prostate cancer, resulting in a rise in the medical use of these drugs. However, recent reports suggest that BPs, particularly the nitrogen-containing BPs pamidronate (Aredia) and zoledronic acid (Zometa), both manufactured by Novartis of East Hanover, NJ, are capable of causing bisphosphonate-associated osteonecrosis of the jaw (BON). With 2.5 million patients treated with pamidronate and/or zoledronate worldwide, BON occurs in about one per 10,000 treated patients (Novartis, unpublished data, 2004). Currently, the total number of reported cases associated with alendronate (Fosamax, Merck and Co. Inc., White-house Station, NJ) the most commonly prescribed oral bisphosphonate, is approximately 170 worldwide (C. Arsvær, oral communication, March 2006). This corresponds to a spontaneous BON incidence of approximately 0.7 cases per 100,000-years exposure. However, there is insufficient data to determine why the osteonecrosis reported seems to particularly affect the jaw, with a slightly higher rate in the mandible than the maxilla. This report concerns the management of a patient with BON. Information provided includes: the pharmacologic properties of the several bisphosphonates currently available; the pathobiological mechanism; the clinical presentation of the oral lesions; and recommendations for the oral management of patients who have received BP therapy, with consideration of a preventative approach based on current knowledge.



BISPHOSPHONATE OSTEONECROSIS LITERATURE

J Oral Maxillofac Surg. 2007 Jul;65(7):1321-7.

Hyperbaric oxygen treatment and bisphosphonate-induced osteonecrosis of the jaw: a case series. Freiburger JJ, Padilla-Burgos R, Chhoeu AH, Kraft KH, Boneta O, Moon RE, Piantadosi CA.

PURPOSE: Bisphosphonate (BP)-associated osteonecrosis of the jaw (ONJ) is an emerging problem with few therapeutic options. Our pilot study of BP-ONJ investigated a possible role for hyperbaric oxygen (HBO(2)) therapy. **PATIENTS AND METHODS:** A total of 16 patients, ranging in age from 43 to 78 years, with BP-ONJ were treated with adjunctive HBO(2) between July 2003 and April 2006. Staging was based on the size and number of oral lesions. Clinical response after treatment and at distant follow-up; the odds of remission, stabilization, or relapse; and time to failure analysis were calculated. **RESULTS:** The median time on BP therapy before appearance of ONJ symptoms was 18 months, and that from symptom onset to HBO(2) therapy was 12 months. Fourteen of 16 patients (87.5%) improved in stage. The size and number of ONJ lesions were decreased after HBO(2) therapy ($P < .001$ and $P = .008$, respectively; Wilcoxon signed-rank test). Immediately after HBO(2) therapy, 7 of 16 patients (44%) were in remission and 8 (50%) had stabilized; however, stabilization without remission was sustained in only 2 patients. At follow-up, 10 of the patients (62.5%) were still in remission or had stabilized. The 7 patients who continued on BP treatment during HBO(2) therapy had a shorter time to failure (8.5 months; 95% confidence interval [CI] = 7.1 to 9.8) than those who discontinued the drug (20.1 months; 95% CI = 17.5 to 23.9; $P = .006$ by the log-rank test). Clinical response was not associated with cancer type or malignancy remission status. **CONCLUSIONS:** Adjunctive HBO(2) therapy may benefit patients with BP-ONJ; however, the outcome is improved with cessation of BP administration.

BISPHOSPHONATE OSTEONECROSIS LITERATURE

Am J Otolaryngol. 2007 May-Jun;28(3):158-63.

Osteonecrosis of the jaws due to bisphosphonate use. A review of 60 cases and treatment proposals. Magopoulos C, Karakinaris G, Telioudis Z, Vahtsevanos K, Dimitrakopoulos I, Antoniadis K, Delaroudis S.

PURPOSE: Bisphosphonates are compounds used in the treatment of various metabolic and malignant bone diseases. In the last two and a half years, there has been a striking increased referral of patients with exposed necrotic jawbone, mostly after several teeth extractions. The only clinical feature common in all patients was the use of bisphosphonates in the treatment of bone diseases. **PATIENTS AND METHODS:** We performed a retrospective multicentric study of 60 patients with necrotic bone lesions of the jaws of various extent from July 2003 to October 2005. The necrotic bone involved the maxilla (37%), the mandible (50%), or both (13%). The bisphosphonate administered was mostly zoledronate. The management of the patients included cessation of bisphosphonate therapy for more than 6 months, long-term antibiotics, hyperbaric oxygen administration in some cases, and various surgical restorative procedures. **RESULTS:** The implementation of the treatment protocol in 7 patients so far lead to high cure rates, whereas surgical restoration of the defect without previous cessation of bisphosphonate therapy had discouraging results. **CONCLUSIONS:** Clinicians and dentists should have in mind this new complication of bisphosphonate administration to identify and treat osteonecrosis of the jaws.

Rev Stomatol Chir Maxillofac. 2006 Dec;107(6):441-4.

A proposed algorithm for medicodental care of patients treated with bisphosphonates Hugentobler M, Richter M.

Bisphosphonates (BP) were first named diphosphonates. They are potent inhibitors of osteoclastic activity and so reduce bone remodeling. Additionally they have anti-angiogenic properties and contribute to progressive disappearance of bony micro-vascular blood supply. Administered orally, BP are generally used to prevent and treat osteoporosis. Injectable BP are used in patients with multiple myeloma and metastatic solid tumors. Scientific evidence dealing with a potentially devastating side effect of BP, osteochemonecrosis of the jaws, is growing rapidly. Clinical signs and symptoms include absent or delayed soft tissue healing with bony exposure following dental extraction or spontaneous gum dehiscence. Patients are usually asymptomatic but may develop pain if the bone becomes secondarily infected. At the beginning, no radiographic manifestations are seen, but in some cases a vast zone of necrotic bone can be seen on MRI, larger than what could be expected. Surgical debridements, bone curettage, local irrigation and or hyperbaric oxygen therapy have proven to be unsuccessful. Up to now, no definitive treatment strategy has been published to manage those patients leaving the dentist or the stomatologist resourceless. This article proposes recommendations for general practitioners, dentists, oral surgeons and designed for three types of patients: 1. patients to be treated with BP; 2. patients treated with BP without bisphosphonate-associated osteonecrosis; 3. patients with bisphosphonate-associated osteonecrosis. The proposed guidelines are not definitive and practitioners remain free to choose their treatment. Of utmost importance is to recognize the risks of oral complications before, during and after surgery in patients treated with BP and to inform them of such risks.

BISPHOSPHONATE OSTEONECROSIS LITERATURE

Int J Hematol. 2006 Nov;84(4):343-5.

Hyperbaric oxygen in addition to antibiotic therapy is effective for bisphosphonate-induced osteonecrosis of the jaw in a patient with multiple myeloma.

Shimura K, Shimazaki C, Taniguchi K, Akamatsu S, Okamoto M, Uchida R, Nomura K, Inaba T, Horiike S, Kanamura N, Taniwaki M.

A 60-year-old man with multiple myeloma (MM) (IgG-kappa, stage IIIA) had been treated with minodronate at 6 mg orally as a phase 1 clinical trial for myeloma bone disease for 13 months (total dose, 4032 mg). Then he received incadronate at 10mg intravenously every 1 to 4 weeks (total dose, 350 mg). In July 2005, he complained of mild right mandibular pain, and bone scintigram showed a hot spot at the right side of the mandible. Panoramic radiograph showed osteonecrosis of the jaw (ONJ) and axial and 3-dimensional computed tomography confirmed ONJ. Oral examination showed massive gingival swelling of the right side of the mandible without exposed necrotic bone. He was given clarithromycin in addition to levofloxacin, followed by hyperbaric oxygen (HBO) therapy, which resulted in the complete disappearance of the pain. This is a first reported case of ONJ induced by incadronate. The present case suggests that early detection of ONJ by regular dental check-ups is important in the management of patients with MM who have received bisphosphonate therapy, and HBO in combination with antibiotic therapy is effective in the early stage of ONJ.

Dent Today. 2006 Aug;25(8):52, 54-7.

Bisphosphonate-associated osteonecrosis of the jaw: conclusions based on an analysis of case series.

Landesberg R, Wilson T, Grbic JT.

ONJ appears to be associated with BPs; however, the pathophysiology, incidence, and co-morbidities require further investigation. The major risk factors identified to date appear to be cancer (or chemotherapy for cancer) and dental procedures or oral trauma. A clear definition of ONJ is critical to understanding this disease entity. Although recommendations regarding the prevention and management of ONJ exist, clinical studies are needed to establish more definitive guidelines for the management of ONJ. The use of intensive hyperbaric oxygen therapy may be beneficial to patients with ONJ.



BISPHOSPHONATE OSTEONECROSIS LITERATURE

Appl Human Sci. 1997 Jul;16(4):143-8.

Bone changes due to hyperbaric exposure.

Aoki H.

Based on the hypothesis that bone calcification is promoted by loading physical pressure, changes in the microstructure of the bone under hyperbaric conditions were analyzed by imaging technology. Hyperbaric exposure was carried out for two weeks at 2 atm (equal to the pressure at a depth of water of 10 m) which was achieved using a mixed gas of helium and oxygen (He:O₂ 88%:12%) in which the oxygen partial pressure was maintained at constant (PO₂: 0.21 bar). In image technological analysis, the growth and development of the bone were evaluated at different stages using Digital Magnification Radiography (DMR) images and based on changes in the X-ray absorption ratio. DMR images after hyperbaric exposure showed calcification in the heads of long bones (humeri, femora, and tibiae) in mice. There were also significant changes in the X-ray absorption ratio in the heads. The accumulation of ^{99m}Tc-MDP was higher in all long-bone heads after hyperbaric exposure than before exposure. These results suggest that the hyperbaric environment promotes bone calcification.