NEWS LETTER

Pharmacotherapy Update

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Osteonecrosis of the Jaw Associated with the Use of Bisphosphonates: Part II

by Kathryn B. Nguyen, Pharm.D.

Introduction: Osteonecrosis of the jaw (ONJ) typically occurs secondary to avascularity caused by radiotherapy for head and neck cancer.[1] However, a number of case reports have recently been published regarding bisphosphonate-induced ONJ. This is the first long-term adverse event described for bisphosphonates and is depicted as a sudden growth of necrotic bone in the oral cavity of patients receiving bisphosphonate therapy.[2] The most common bisphosphonates reported to be associated with ONJ are pamidronate (Aredia®) and zoledronic acid (Zometa®).

Please see Pharmacotherapy Update Volume IX, No. IV, July/August 2006 for Part I, which focuses on the mechanism of bisphosphonate-induced ONJ, clinical presentation, incidence and risk factors of ONJ, select case series, and radiographic and histopathologic findings.

Part II consists of the management of ONJ.

Management of ONJ: The management of patients with ONJ involves more than symptomatic treatment. Extensive preventive measures must be taken to ensure that patients obtain the necessary work-up before starting bisphosphonate therapy, including full dental assessment and treatment plan. If therapy can be postponed without the risk of skeletal damage, teeth likely to create problems should be extracted and all surgical procedures should be finished before the start of therapy.[1,4,28,29,39] The surgical procedures to remove existing dental problems may include tooth removal, periodontal surgery, root canal treatment, caries control, dental restorations, and dentures.[28] In patients who require dental treatment before starting bisphosphonate therapy, antibiotic prophylaxis is needed for invasive procedures.[28] Penicillin is the drug of choice for prophylaxis; however, fluoroquinolones, metronidazole, or erythromycin may be used in patients with a penicillin allergy.[28] Some authors suggest delaying bisphosphonate therapy for at least 1 to 3 months if an invasive procedure has been done to allow for healing.[28] After the procedure, bisphosphonates should not be initiated until the oral wound has healed.[6] Once bisphosphonate therapy is started, regular dental assessment should be adopted and patients should be educated about proper oral hygiene.[1,33] The monitoring plan for patients who have been on bisphosphonate therapy should entail limited non-surgical periodontics and endodontics to manage dental decay, periodontal disease, and periapical inflammation as well as restorative dentistry.[1]

In regards to the consequences of ONJ, there was a difference in morbidity between patients that received IV compared to oral bisphosphonates. Most patients who were given IV bisphosphonates remained with permanent disability and those patients treated with oral bisphosphonates often healed from the complications of ONJ.[1] The goal of treatment in these patients is to control the infection and alleviate the patient's pain.[1] Treatments such as 0.12% chlorhexidine (Peridex®) mouth rinse, systemic antibiotics, surgical debridement, and hyperbaric oxygen have been used (see Table 3). Some of these treatments are efficacious in patients while others have not improved and may have even worsened their condition. Some recommendations for antibiotic treatment include long-term or possibly a permanent course of penicillin or metronidazole alone, or in combination.[28] Ciprofloxacin or erythromycin along with metronidazole can be used in patients with a penicillin allergy.[28] For patients that are symptomatic or have regions of necrotic bone not responsive to irrigations and antibiotics, surgical debridement may also be an option.[10] Finally, hyperbaric oxygen has not been found to be efficacious in any reported case.[39] It is also important to discuss the discontinuation of IV bisphosphonate therapy with all involved parties (i.e., oncologists, dentists, primary care physicians, etc).[29] However, it has been reported that ONJ does not resolve even after discontinuation of IV bisphosphonate therapy.[4]

The current recommendation by the National Comprehensive Cancer Network for using bisphosphonates in multiple myeloma patients is to monitor for ONJ.[40] No other specific recommendations are listed. Recommendations by the American Dental Association for managing patients on bisphosphonate therapy are listed in Tables 4 and 5.[41] Oral antibiotics may be used if the patient has unexpected pain, purulence or active sequestration after dental procedures. However, it is important to recognize that these recommendations are not supported by any controlled studies in patients with bisphosphonate-induced ONJ and that they are expert opinions based on the treatment of oral infections of bone in other dental situations.[41]

Summary: The majority of patients in case reports of bisphosphonate-induced ONJ have a common history of

Table 3. Histopathology and Treatment

Author	Radiography/Histopathology Performed (# of patients)	Treatment (# of patients)
Ficarra et al.[4]	Yes (7)	Cessation of bisphosphonates, Antibiotics (9), Debridement (9)
Bagan et al.[32]	Yes (10)	Antibiotics (10), Periodic debridement
Dimitrakopoulos et al.[8]	Not specified	Cessation of bisphosphonates, Antibiotics, Hyperbaric oxygen, Debridement, Sequestrectomy
Purcell et al.[7]	Not specified	Not specified
Pires et al.[33]	Yes (12)	Antibiotics (3), Antibiotics and debridement (11)
Cheng et al.[1]	Yes (2)	Hyperbaric oxygen/re-section (1), Re-section (1), Hyperbaric oxygen/curettage (1), Curettage (6) , Non-surgical (6), Antibiotics (not specified)
Thakkar et al.[6]	Not specified	Antibiotics (17)
Migliorati et al.[27]	Yes (12)	Antibiotics (17), Sequestrectomy (14), Hyperbaric oxygen (1)
Farrugia et al.[5]	Not specified	Antibiotics (22), Local debridement (13), Both (13), Partial maxillectomy (1), Hyperbaric oxygen (1)
Ruggiero et al.[10]	Not specified	Sequestrectomy (44), Mandibulectomy (10), Maxillectomy (7), Conservative management (2)
Marx et al.[28]	Yes (87)	Antibiotics (97)

Time to onset: 1 week – > 2 years
Radiography/Histopathology: signs of bone necrosis & chronic osteomyelitis
Culture: *Actinomyces isareli*, *Escherichia coli*, *Bacteroides melaninogenicous*, normal flora
Medications used: clindamycin, amoxicillin/clavulanate, penicillin G, 0.12% chlorhexidine

malignant diseases including both solid tumor and hematological disorders. None of the patients had previously received radiation therapy to the head and neck region, which often account for osteoradionecrosis. However, most patients were actively receiving chemotherapy or had previously received chemotherapy for their respective malignancies.

It is ideal for all patients with cancer, who may be initiated on a bisphosphonate to obtain a dental assessment. Collaboration between the medical oncologist and dentist is vital in minimizing the morbidity of ONJ. For patients receiving oral bisphosphonates for osteoporosis, the primary care physician and dentist must work together on the patient's care and adhere to the ADA recommendations. Close monitoring of patients receiving either oral or IV bisphosphonates is required. Although there are not enough data to prove an association between the use of bisphosphonates and ONJ, there have been enough reports published to encourage clinicians to monitor and report this adverse effect.

Table 4. American Dental Association (ADA)[41]
Expert Panel Recommendations For Managing Patients Receiving Oral Bisphosphonate Therapy

General recommendations	• Routine dental exams • Comprehensive oral evaluation for all patients beginning therapy with oral bisphosphonates. • Inform the patient taking oral bisphosphonates that there is a low risk of developing ONJ, and good oral hygiene along with regular dental checkups lowers the risk. • Patients should be educated to contact the dentist if any problems develop in the oral cavity. • In addition, the patient should be informed of the dental treatment needed; other risks involved with these various treatments, and the risk of not receiving treatment, even temporarily. • ONJ can occur spontaneously. However, patients with possible risk factors for bisphosphonate-associated ONJ may benefit from evaluation by an expert in metabolic bone diseases. • Before an invasive procedure, patients should be informed about the implications of oral bisphosphonate therapy and the risk of ONJ. • Treat any periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis, and active abscesses immediately.
Recommendations for other dental procedures	• Please refer to the ADA recommendations

Table 5. ADA Antibiotic Recommendations for Treatment of Oral Infections[41]

Patient Type	Suggested Drug	Oral Regimen
Patients not allergic to penicillin	Amoxicillin or Metronidazole*	500 mg TID x 14 days 250 mg TID x 14 days
Patients allergic to penicillin	Clindamycin or Azithromycin	300 mg TID x 14 days 250 mg daily x 10 days

*May be combined with amoxicillin
TID: three times daily

New Drugs

Opana®:
On June 22, 2006, the Food and Drug Administration (FDA) approved a new formulation of oxymorphone, a narcotic analgesic. The brand name of the new oral formulation is Opana® which is available as immediate-release (IR; 5- and 10-mg) and extended-release (ER; 5-, 10-, 20-, and 40-mg) tablets. Oxymorphone (brand name Numorphan®) has been available as an injectable (1 mg/ml and 1.5 mg/ml) and rectal suppository (5 mg).

Opana® is indicated for moderate-to-severe pain and is a Schedule II narcotic. The IR formulation is dosed as 10 to 20 mg every 4 to 6 hours while the ER tablets should be dosed every 12 hours. Opana® ER can be initiated at 5 mg every 12 hours with doses titrated in increments of 5 to 10 mg every 12 hours every 3 to 7 days. Both IR and ER tablets should be taken 1 hour before or 2 hours after eating.

Both Numorphan® and Opana® are currently non-formulary for inpatient use at the Cleveland Clinic. When prescribing oxy*morphone* for outpatient use, be cautious not to confuse with oxy*codone*.

Daytrana™:
Daytrana is a transdermal formulation of methylphenidate from Shire Pharmaceuticals. It was approved by the FDA in April 2006 and the patch is available as 10-, 15-, 20-, and 30-mg/9 hours. It should be applied to the hip once daily 2 hours before a therapeutic effect is required and removed after 9 hours, although it can be removed before 9 hours. The dose should be initiated at 10 mg for 1 week and titrated up in weekly intervals until a desired response is attained. Some potential issues of Daytrana™ include: redness at the site of application, sensitization to methylphenidate, and early removal of the patch by children. Daytrana™ is currently non-formulary for inpatient use at the Cleveland Clinic.

Qualaquin™:
Recently, a new brand of quinine sulfate was approved by the FDA. Qualaquin™, available as 324 mg capsules, is now the only FDA-approved quinine sulfate product on the market (since the other quinine products came on the market before FDA approval was required). Now that Qualaquin™ is available, other quinine products will need to be approved or be taken off the market.

Qualaquin™ is only indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria. It is not approved for patients with severe or complicated *P. falciparum* malaria, prevention of malaria, or prevention of nocturnal leg cramps. The dose is two capsules (648 mg) every 8 hours for 7 days and it should be taken with food to decrease gastric upset. Qualaquin™ is currently non-formulary for inpatient use at the Cleveland Clinic.

Did You Know…?
Warfarin and Cranberry Juice Interaction

Recently, there have been increasing case reports of possible drug interactions between warfarin (Coumadin®) and cranberry juice. The ingestion of cranberry juice is thought to alter the INR in patients taking warfarin. Although the mechanism of action is not fully understood, it is **not** believed to be due to the vitamin K content of cranberries, rather there are other postulated theories. One mechanism of action involves salicylic acid, which is a constituent of cranberries. It is thought that salicylic acid in cranberries could have an additive effect on the anticoagulant activity of warfarin. A second mechanism of action involves flavonoids. Flavonoids are thought to have a wide range of pharmacological activities and certain flavonoids may inhibit warfarin metabolism by inhibition of the cytochrome P450 (CYP) 2C9 isoenzyme.

There is currently only minimal information available regarding this potential interaction between warfarin and cranberry juice, however Barr Laboratories does document the interaction in the Coumadin® prescribing information. Three case reports, as well as 12 interactions between cranberry juice and warfarin have been reported to the United Kingdom's Committee on Safety of Medicines as of October 2004. With this information, it is recommended to inform patients taking Coumadin® that the use of cranberry juice be reduced or eliminated. If there is a medical need for the use of cranberry juice, careful and frequent monitoring of the INR as well as the signs and symptoms of bleeding should be performed and dosages should be adjusted accordingly. Additionally, an interaction may occur if a patient increases the intake of cranberry juice or occasionally ingests a large volume, but it is unknown if this interaction can be avoided by separating doses or limiting the consumption of cranberry juice. Finally, at this time, it is not known if this warfarin interaction can only occur with cranberry juice or if other cranberry products (e.g., cranberry extract tablets) or cranberries can also cause an interaction. For a review of the literature, please read the following recent publication: Aston JL, et al. Pharmacotherapy 2006;26(9):1314-9.

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Formulary Update

The Pharmacy and Therapeutics Committee met in October 2006, and the following decisions were made:

1. **Selegiline Transdermal Patch (Emsam®)**: Emsam® is an irreversible inhibitor of monoamine oxidase (MAO-I) indicated for the treatment of major depressive disorder. At low doses, it selectively inhibits type B MAO (MAO-B); at higher doses it inhibits both type A MAO (MAO-A) and MAO-B. Due to the risk of serotonin syndrome, Emsam® has several contraindications including, but not limited to, concomitant administration with selective serotonin reuptake inhibitors; dual serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, and meperidine. To decrease the risk of developing hypertensive crises, patients receiving Emsam® at doses exceeding 6 mg/24 hours should avoid foods rich in tyramine (e.g., aged cheeses and meats). The recommended starting dose and target dose of Emsam® is 6 mg/24 hours. If needed, dosage increases in increments of 3 mg/24 hours should be made at intervals of no less than 2 weeks. The patch should be applied to dry, intact skin on the upper torso, upper thigh, or outer surface of the upper arm once every 24 hours. Emsam® is available as a 20 mg patch (6 mg/24 hours), 30 mg patch (9 mg/24 hours), and 40 mg patch (12 mg/24 hours). Its use is ***restricted*** to the Department of Psychiatry and the Headache Center.

2. **Levetiracetam Injection (Keppra® Injection)**: Intravenous levetiracetam was recently FDA-approved as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy where oral therapy is not feasible. Its mechanism is currently unknown. The recommended initial dose for partial onset seizures is 500 mg IV twice daily. This dose may be increased every 2 weeks by 1000 mg/day to a maximum dose of 3000 mg/day. There is no evidence that doses >3000 mg/day provide any additional benefits. Dosage reductions are recommended in patients with impaired renal function. When switching from oral levetiracetam therapy to injection, total daily doses should be the same. Levetiracetam injection is ***restricted*** to the Departments of Neurology and Neurosurgery and the Epilepsy Monitoring Unit for patients having acute seizures, suspected or confirmed status epilepticus, or those who are unable to receive oral medications.

3. **Ranolazine (Ranexa™)**: Ranolazine has antianginal and anti-ischemic effects that are not dependent upon reductions in heart rate or blood pressure. Indicated for the treatment of chronic angina, it is a partial fatty acid oxidase inhibitor that stimulates cardiac glucose oxidation and increases ATP production thereby maintaining myocardial function when myocardial oxygen delivery is reduced. It should be used in combination with amlodipine, beta-blockers, or nitrates. Ranolazine can prolong the QTc interval in a dose-related manner as well as significantly increase serum levels of simvastatin and digoxin. Initial dosing is 500 mg orally twice daily and may be increased to a maximum of 1000 mg orally twice daily. **Due to significant drug interactions and the potential for QTc prolongation, all orders (i.e., new orders and continuation of home therapy) for ranolazine must be reviewed by Cardiovascular Clinical Pharmacy Specialists prior to dispensing**.

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Department of Pharmacy/Hb-03
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