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Bisphosphonates and ONJ: Risks, Benefits, and Prevention

A few years ago, several major news publications published articles regarding the risk of osteonecrosis of the jaw (ONJ) for patients taking drugs called bisphosphonates. These articles, along with several lawsuits filed against the pharmaceutical companies manufacturing these drugs, purport the dangerous nature of bisphosphonates and exaggerate the likelihood of ONJ. This, in turn, has raised concern among many patients taking bisphosphonates.

ONJ is a condition affecting the bones of the jaw - usually the lower jaw. The condition may resemble other types of dental disease, and often causes symptoms such as: pain in the teeth and jaw, loosening of teeth, infection, swelling, and draining. ONJ may initially show no symptoms for several months.

The estimated occurrence of ONJ in persons taking oral bisphosphonates {**Fosamax**[®] (Alendronate), **Actonel**[®] (Risedronate), **Boniva**[®] (Ibandronate)} is extremely low, roughly 0.7 cases per 100,000 person-years exposure. These cases represent only 6% of all bisphosphonate related ONJ occurrences. Cancer patients receiving intravenous bisphosphonates have a reported 6-10% rate of developing ONJ, and these cases make up 94% of all reported bisphosphonate related instances of ONJ. When considering these risks, it is important to note that osteoporosis, left untreated, is estimated to cause at least one fracture (wrist, hip, or spine) in one of every two women during their lifetimes. These osteoporotic fractures can be debilitating and contribute to a significant number of hospitalizations, institutionalizations, and deaths. Furthermore, a recent analysis on data from the Women's Health Initiative (WHI) demonstrated a 32% decrease in breast cancer cases in women taking oral bisphosphonates compared to women not taking the drugs. Although this data is preliminary and must be confirmed with further studies, it is an encouraging and possibly important development.

Oral bisphosphonates are used to prevent bone loss and fractures. Bisphosphonates improve bone health by reducing bone turnover, a process by which the bone "remodels" itself, allowing elasticity of the bone, repair of microfractures and proper distribution of calcium. During the bone remodeling cycle, the collagen and mineral in the bone are first broken down, a process called resorption, and then the bone is reformed and restored to its normal mass. In osteoporosis, too much bone is resorbed and not enough synthesized/formed. This results in thin, brittle, fragile bones, which fracture easily. Bisphosphonates limit the entire process of bone turnover, by inhibiting resorption.

The risk for ONJ is highest for patients who have been treated for metastatic breast cancer and multiple myeloma as these patients are likely to receive high doses of intravenous bisphosphonates. This allows a very large amount of bisphosphonate - 50% of the administered dosage - to be absorbed directly into the bone. In contrast, the percentage absorbed from oral doses is only about 1%. The small absorption rate lowers the overall impact of the drug and appears to decrease the risk of developing ONJ. An individual's risk may be increased by certain factors, including age (over 65

years), use of glucocorticoids (cortisone-like medications) and/or estrogen, previous periodontal disease, other causes of poor oral hygiene, and invasive recent dental procedures (i.e. tooth extractions).

While the risk for developing ONJ is already extremely low, this risk can be lowered by simply maintaining good oral hygiene and seeing a dentist regularly. It is also recommended that patients who are about to begin oral bisphosphonate treatment should obtain a thorough oral evaluation by a dentist. Once taking bisphosphonates, if dental treatment, other than routine check-ups, is required, alternative or non-surgical treatment should be considered above surgical or invasive procedures, if possible. Using antibiotics before and after dental procedures may also reduce the risk of dangerous infections. While some dentists may advise stopping bisphosphonate treatment in the months before a dental procedure, it has not been proven that this has any effect on the risk of developing ONJ.

Total numbers ONJ cases reported (as of 7/1/06) in association with orally administered nitrogen-containing bisphosphonates:

170 cases with Alendronate (**Fosamax**[®], Merck and Co., inc.)

20 cases with risedronate (**Actonel**[®], Procter and Gamble)

1 case with ibandronate (**Boniva**[®], Roche)

References:

Rosen, Clifford J. and Tenenhouse, Alan. "Biochemical Markers of Bone Turnover: A Look at Laboratory Tests that Reflect Bone Status". Available at:
http://www.postgradmed.com/issues/1998/10_98/rosen.htm. (06/29/06).

Van Staa, T.P. et al. "Use of Oral Corticosteroids and Risk of Fracture". Van Staa, T.P. et al. *Journal of Bone and Mineral Research*. Vol. 15: 6. 2000.

Sook-Bin Woo, Hellstein, John W., and Kalmar, John R. "Systematic Review: Bisphosphonates and Osteonecrosis of the Jaw". *Annals of Internal Medicine*. May, 2006 Vol. 144: 753-761.

Edwards, Beatrice J, et al. "Expert Panel Recommendations: Dental Management of Patients on Oral Bisphosphate Therapy". *Report of the Council on Scientific Affairs, American Dental Association*. June, 2006.

Carreyrou, John. "Fosamax Drug Could Become Next Merck Woe". *The Wall Street Journal*. April 12, 2006.

Kolata, Gina. "Drug for Bones Is Newly Linked to Jaw Disease". *The New York Times*. June 2, 2006.

Rabin, Roni Caryn. "Bone Drugs Taken by Some Women May Lower Breast Cancer Risk, Studies Say". *The New York Times*. December 10, 2009.

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