



Osteoporosis Canada

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## Osteonecrosis & Bisphosphonate position statement

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Response to "Use of oral bisphosphonates and the Risk of Aseptic Osteonecrosis: A Nested Case Control Study" by Etminan, Aminzadeh, Matthew and Brophy and published online in the *Journal of Rheumatology* - January 2008.

Osteonecrosis of the jaw in association with bisphosphonate use has been discussed at length in the medical and lay press over the past year. Previous data have suggested that the localized death of bone in the jaw has occurred predominantly in the setting of intravenous bisphosphonate use in the cancer population where it is recognized that the patients are ill, have often undergone a variety of chemotherapies for their malignancy and that the bisphosphonate medications have been used in significantly higher doses than those used in our more conventional osteoporosis population. The role of poor baseline dental hygiene has also been highlighted. While there have been reports in the literature of osteonecrosis of the jaw in the osteoporosis population both on and off bisphosphonates, these reports have been rare. As such, the recent study published online in the *Journal of Rheumatology* which examines the risk of developing aseptic osteonecrosis at any site in the presence of past or current use of this class of medication is of great interest.

The recent study looks at data from administrative data bases in Quebec and selected a retrospective cohort of nearly 90,000 patients, all of whom had been hospitalized for procedure based cardiac assessment/treatment between 1995 and 2002. Within this group, the database was analyzed to determine the subset of patients for whom a diagnosis of Osteonecrosis had been made. This information was then matched to the data obtained through the provincial drug formulary records to identify which of the patients diagnosed with osteonecrosis had been/were taking oral bisphosphonate medication, specifically alendronate, etidronate or risedronate. Statistical analysis was then carried out with the conclusion that osteonecrosis at any

site was approximately three times more common in those individuals who had ever or were currently taking an oral bisphosphonate medication.

Taken at face value, the conclusion raises concern.

The authors do list a number of important limitations in their study including lack of verification of the diagnosis of osteonecrosis - clearly important in determining the validity of their conclusion.

Additionally, the two groups had substantial and potentially important differences - aside from the presence of osteonecrosis. The authors indicate that prednisone use was higher in the target group on bisphosphonates (18% vs 5 %). Additionally, they also note that in this population of patients, the bisphosphonate taking cohort had higher co-morbidity and more malignancies. Use of corticosteroids and a number of illnesses are known etiological factors in the development of osteonecrosis so mismatches between the case and the control groups could have significant impact in the cause and occurrence of osteonecrosis and hence, substantially influence the conclusions of the study.

Finally, many methodologic and statistical concerns may be raised. For example the coding to diagnose avascular necrosis may not have been validated and the data itself was taken from a pre-existing cardiac database and used only hospital diagnostic codes which could have influenced the results positively or negatively. Avascular necrosis of the hip and osteonecrosis of the jaw could not be distinguished from the diagnostic codes. Rate ratios were adjusted for imbalances between the groups. However without seeing the unadjusted analysis, we really do not know how the joint adjusted effects of both corticosteroids and bisphosphonates may have been affected. Indeed, as has been pointed out bisphosphonate use may simply be coincidental, a matter of guilt by association.

While this study has put forward an interesting postulate, it is evident that there are major limitations in the study and the inter-relationship between osteonecrosis and bisphosphonate use remains unclear and likely, multi-factorial. More analysis of the data set particularly attempting to verify the diagnosis and type of osteonecrosis should have been attempted. The whole of this analysis depends on it! What isn't in question is the high prevalence of low trauma fractures in our older population, the fracture-associated morbidity and mortality in this group and the significant reduction of clinical fractures with the use of bisphosphonates. In the high risk individual with osteoporosis, the known benefits of treatment frequently far outweigh the concerns that have been raised.