



## PIC QUESTION OF THE WEEK: 02/25/08

Q: Please explain the supposed association between bisphosphonates and atrial fibrillation.

A: In the United States, millions of post-menopausal women suffer from osteoporosis. Bisphosphonates have recently become the mainstay for prevention and treatment of this disease. Many studies have shown that this class of medication increases bone mass and reduces the risk of fractures. The most recent drug added to this group is zoledronic acid (*Reclast*). It was approved by the FDA in August of 2007 and is labeled for once-yearly intravenous (I.V.) infusion. Other bisphosphonates labeled for management of osteoporosis include alendronate, ibandronate, and risedronate. Adverse effects associated with all bisphosphonates include gastrointestinal disturbances, esophageal erosion, musculoskeletal pain, ocular inflammation and, rarely, osteonecrosis of the jaw. Recent attention has been directed to a possible association between bisphosphonates and atrial fibrillation. A clinical trial evaluating once yearly use of I.V. zoledronic acid versus placebo identified a frequency of atrial fibrillation of 2.4% while the incidence in the placebo group was 1.9%. The majority of these events occurred more than 30 days after infusion of zoledronic acid or placebo. An earlier study comparing oral alendronate to placebo resulted in a 1.5% frequency of atrial fibrillation in the active treatment group and 1% of those getting placebo. There was no statistical difference in either study between the frequency of atrial fibrillation and the administration of drug or placebo. Suspected mechanisms for a *possible* association between parenteral bisphosphonates and atrial fibrillation include changes in serum calcium levels and possible increases in inflammatory cytokines. Oral and parenteral administration of bisphosphonates produce a decrease in serum calcium levels; however, it is unknown if oral administration enhances release of cytokines. The FDA has evaluated this data and suggests that patient age may have been related to the development of atrial fibrillation. The risk of this arrhythmia increases with age and patients included in these studies generally exceeded 65 years. The FDA has reviewed post-marketing reports and did not identify any population of bisphosphonate users to be at a significantly higher risk for this adverse effect. The FDA continues to collect data on the possible association between the use of bisphosphonates and atrial fibrillation. At this time, the agency does not feel enough data is available to make any changes in the product literature or provide any warning regarding this class of medications and an increased risk of atrial fibrillation.

### References:

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- Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. *N Engl J Med* 2007;356:1895-6.
- Food and Drug Administration. Early communication of an ongoing safety review. [http://www.fda.gov/cder/drug/early\\_comm/bisphosphonates.htm](http://www.fda.gov/cder/drug/early_comm/bisphosphonates.htm). Accessed February 18, 2008.

Rachael L. Slogan and Kevin M. Kunkle, Pharmacy Clerkship Students

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