

Bisphosphonates Tied to Cancer, Osteonecrosis

BY DAMIAN McNAMARA

Miami Bureau

Use of oral bisphosphonate drugs is associated with an increased risk of esophageal cancer, according to reports in the United States, Europe, and Japan.

Multiple agents in the class are associated with the esophageal cancer warning, which was raised by an epidemiologist at the Food and Drug Administration in a letter to the *New England Journal of Medicine*.

Between October 1995, when alendronate (Fosamax) was first approved by the FDA, and May 2008, the agency has received reports of 23 patients taking the drug diagnosed with esophageal cancer. This includes 21 cases where oral alendronate was the suspect drug and 2 where concomitant use of the agent was implicated, Diane K. Wysowski, Ph.D., wrote (*N. Engl. J. Med.* 2009;360:89-90).

Of the 23 patients, 18 (78%) were women and the median age was 74 years. The median time from alendronate use to diagnosis was 2.1 years (based on 16 patients).

One patient took alendronate despite having Barrett's esophagus, a precursor of esophageal adenocarcinoma, pointed out Dr. Wysowski, of FDA's Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research. She reported no relevant disclosures.

Merck, which manufactures alendronate, said in a statement that "the incidence of esophageal cancer in the general population increases with age and is reported to be more common in the older population. According to U.S. statistics from the National Cancer Institute, the annual incidence of esophageal cancer in the

population aged 65 years or older is 22.3 per 100,000."

The statement also noted that "data from Merck's clinical trials of Fosamax and from postmarketing reports do not suggest any association between alendronate and esophageal cancer. Fosamax has been studied in controlled clinical trials involving more than 17,000 patients, contributing as much as 10 years' data."

The FDA's adverse event reporting database did not include any reports of esophageal cancer associated with other bisphosphonates. In contrast, reports for 31 patients in Europe and Japan included a diagnosis of this cancer following use of alendronate, risedronate (Actonel, Procter & Gamble), ibandronate (Boniva, Roche), and/or etidronate (Didronel, Procter & Gamble).

Twenty-two patients (71%) were women and the median age was 69 years. The median time from drug exposure to diagnosis was 1.3 years (based on 21 patients). Barrett's esophagus was diagnosed in three patients.

The distal esophagus was affected in eight patients (with gastric involvement in four).

An association between esophagitis and oral bisphosphonates is suggested in studies (*Radiology* 1998;206:389-91; *N. Engl. J. Med.* 1996;335:1016-21), "usually when the drugs are not taken according to directions," Dr. Wysowski wrote.

A second published report extends the link between use of bisphosphonates and jaw necrosis to the oral preparation of the agents, which had heretofore been thought to be without this risk. Although researchers previously demonstrated an elevated risk of osteonecrosis of the jaw (ONJ) with intravenous bisphosphonates (*J. Oral Maxillofac. Surg.* 2004;62:527-34), the

current study is the first to show a similar elevated risk with long-term use of an oral agent. Parish P. Sedghizadeh, D.D.S., and his associates at the University of Southern California, Los Angeles, launched the study after evidence suggested the rate of ONJ secondary to alendronate treatment was higher at their institution than that reported by the manufacturer.

In 2006, Merck estimated incidence of this adverse outcome as 0.7 per 100,000 person-years of alendronate exposure, or 170 cases worldwide. An American Dental Association (ADA) expert panel cited this figure when stating that oral bisphosphonate use should not trigger modification of routine dental treatment (*J. Am. Dent. Assoc.* 2006;137:1144-50; *J. Am. Dent. Assoc.* 2008;139:1674-7).

Tooth extraction seems to be a significant trigger of jaw necrosis in patients on long-term bisphosphonates.

Dr. Sedghizadeh and his colleagues identified 208 patients with a history of alendronate in their electronic medical record system. This group included nine patients with active ONJ undergoing treatment at the University of Southern California clinics. The nine represented 1 in 23 of the patients taking alendronate, or about 4% of the study population.

"Most of the patients receiving alendronate at USC who developed ONJ did so after routine tooth extraction, suggesting that perhaps these patients should be identified as an at-risk population and preventive measures should be taken," the authors wrote. The investigators had no relevant disclosures.

Merck released a written statement saying that the study "has material methodological flaws and scientific limitations, making it unreliable as a source for valid scientific conclusions regarding the prevalence of ONJ in patients taking alendronate." The statement said that "In controlled clinical trials involving more than 17,000 patients ... there have been no reports of ONJ." ■

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Vitamin D Deficiency Affects Type 1 Youth

BY HEIDI SPLETE

Senior Writer

Youth with type 1 diabetes are at significant risk for vitamin D deficiency, based on results of a study of 128 children and adolescents.

Chronic vitamin D deficiency in childhood contributes to bone deformity and reduced bone mass, which could increase fracture risk in adulthood. Because previous research suggests that type 1 diabetes itself is associated with reduced bone mineral density, children and teens with type 1 diabetes may be at even greater risk for skeletal weakness, Dr. Britta M. Svoren of the Joslin (Mass.) Diabetes Center and colleagues noted in the *Journal of Pediatrics* (2009;154:132-4).

In this study, the researchers measured serum 25-hydroxyvitamin D (25[OH]D) in infants, children, and teens younger than 18 years with type 1 diabetes in the United States. Vitamin D sufficiency, insufficiency, and deficiency were defined as 25(OH)D levels of 30 ng/mL or higher, 21-29 ng/mL, and 20 ng/mL or lower, respectively.

Overall, only 31 participants (24%) met the criteria for sufficient vitamin D, while 78 (61%) had insufficient vitamin D, and 19 (15%) were vitamin D deficient.

When the children were divided into three age groups, 22% of adolescents aged 12-18 years were vitamin D deficient, compared with 12% of those aged 0-5 years and none of the children aged 6-11 years.

After investigators controlled for factors including age, sex, ethnicity, body mass index, and diabetes control (based on hemoglobin A_{1c} measures), older age was significantly associated with lower 25(OH)D concentrations, and the mean 25(OH)D concentration was significantly

lower in the oldest age group (12-18 years) at 24.2 ng/dL, compared with the youngest age group (0-5 years) at 30.8 ng/dL; those aged 6-11 years were in the middle with a mean 25(OH)D concentration of 26.8 ng/dL.

Ethnicity also was associated with lower 25(OH)D levels, which were significantly more common among nonwhites.

Adolescents with type 1 diabetes have additional risk factors for skeletal weakness, including hyperglycemia and hypercalciuria. Lifestyle factors such as drinking less milk and getting less sun exposure also can play a role. Consumption of sugar-free colas, which is common in teens with diabetes, is an additional risk factor for poor bone health because the beverages contain phosphoric acid, "which is known to reduce intestinal calcium absorption," Dr. Svoren and her associates said.

"Many of these risk factors may not be modifiable because of the inherent presence of diabetes mellitus, [so] ensuring vitamin D sufficiency throughout childhood and during the time of maximal bone mineral accrual seems particularly warranted in this population," they said.

Dr. Svoren and colleagues said that providers should monitor vitamin D in youth with type 1 diabetes and consider vitamin D supplements for those who aren't getting enough vitamin D through their diets.

The results support findings from previous studies showing evidence of vitamin D deficiency in children and adolescents with type 1 diabetes, but more research is needed to confirm the findings and identify the causes of vitamin D deficiency in this population, they said.

The study was funded by grants from the National Institutes of Health, the Charles H. Hood Foundation, and Eli Lilly & Co. The researchers reported that they had no relevant financial conflicts to disclose. ■

Older Black Women Do Have Osteoporosis

RIO GRANDE, P.R. — Approximately one in four elderly black women have osteoporosis, findings from a small study suggest.

Physicians should not ignore the possibility of osteoporosis in their older black female patients, although these women are not usually considered at high risk, compared with other demographic groups, said Dr. Sally P. Weaver, research director of the McLennan County Medical Education and Research Foundation, Waco, Tex.

Previous studies of osteoporosis in women have focused mainly on white women because of evidence of an elevated risk for osteoporosis in that population. Yet older women of any ethnicity are prone to age-related fractures if their bone mineral density (BMD) is low, she said in an interview.

Dr. Weaver and colleagues measured BMD scans from the electronic health records of 44 black women aged 70 years and older. Patients with conditions that could affect bone turnover, vitamin D absorption, or calcium absorption were excluded from the study.

About 50% of the study participants met the criteria for osteopenia and 10% met the criteria for osteoporosis at the left femoral neck. Approximately 25% met criteria for osteopenia or osteoporosis at the lumbar spine. Overall, the left femoral neck had the lowest regional BMD, with an average T score of -1.23. Dr. Weaver presented the results in a poster at the annual meeting of the North American Primary Care Research Group.

Dr. Weaver had no financial conflicts to disclose.

—Heidi Splete