More on Reports of Esophageal Cancer with Oral Bisphosphonate Use

TO THE EDITOR: In her letter to the editor, Wysowski (Jan. 1 issue)[1] notes that the Food and Drug Administration (FDA) received reports of 23 cases of esophageal cancer in patients who had received oral bisphosphonates, and she calls for studies that investigate whether bisphosphonate use is associated with an increased risk of this cancer. The reported cases of esophageal cancer occurred after a relatively short duration of use, with a median time to diagnosis of 2.1 years.

Using data from national registers (1995 through 2005), we individually matched 13,678 patients with fracture who had filled more than one prescription for any oral bisphosphonate (62% for alendronate, 36% for etidronate, and 2% for ibandronate, risedronate, or clodronate) with 27,356 patients with fracture who did not fill any bisphosphonate prescriptions and who were similar with respect to age (mean [±SD], 74.3±8.8 years), sex (89.1% were women), and fracture type. We used a Cox proportional-hazards model that controlled for the Charlson index and the number of concomitant medications, incorporating the time to an event, death, or the end of the study. The study had a median follow-up time of 2.2 years (mean, 2.8) and a median duration of exposure to oral bisphosphonates of 1.5 years (mean, 2.1). We identified 37 cases of esophageal cancer and 48 cases of gastric cancer over a period of 128,300 patient-years. Patients receiving oral bisphosphonates were not at increased risk for esophageal cancer or gastric cancer (hazard ratio for the combined outcome, 0.78; 95% confidence interval [CI], 0.49 to 1.26). The risk of esophageal cancer was significantly reduced (hazard ratio, 0.35; 95% CI, 0.14 to 0.85; P=0.02), whereas the risk of gastric cancer did not differ significantly from that among control subjects (hazard ratio, 1.23; 95% CI, 0.68 to 2.22; P=0.49).

Our study had several limitations. First, although it was a large study, the cancer rates were low, so the confidence intervals were wide. Second, oral bisphosphonates may have been targeted preferentially to and accepted by patients without upper gastrointestinal symptoms, leading to low risks. Third, the hazard ratios may have been overestimates, since the use of endoscopy is more likely in patients who receive oral bisphosphonates. Nonetheless, this national cohort study does not provide support for the suspected increase in the risk of esophageal cancer early in the course of oral bisphosphonate therapy.

Bo Abrahamsen, M.D., Ph.D.
Copenhagen University Hospital Gentofte
DK-2900 Hellerup, Denmark
b.abrahamsen@physician.dk

Pia Eiken, M.D., Ph.D.
Hillerød Hospital
DK-3400 Hillerød, Denmark

Richard Eastell, M.D.
University of Sheffield
Sheffield S5 7AU, United Kingdom

Dr. Abrahamsen reports receiving consulting fees from Novartis, advisory-board fees from Amgen and Nycomed, and lecture fees from Eli Lilly and Procter & Gamble; Dr. Eiken, receiving advisory-board fees from Amgen; and Dr. Eastell, receiving consulting or advisory-board fees from Amgen, Novartis, Procter & Gamble, Servier, Ono Pharmaceutical, and GlaxoSmithKline, lecture fees from Eli Lilly, and grant support from AstraZeneca, Procter & Gamble, and Novartis. No other potential conflict of interest relevant to this letter was reported.

1. Wysowski DK. Reports of esophageal cancer with oral bisphosphonate use. N Engl J Med 2009;360:89-90.

TO THE EDITOR: Wysowski states that 23 cases of esophageal cancer among persons receiving oral bisphosphonates have been reported to the FDA since 1995. We compared the rates of esophageal cancer among persons receiving oral bisphosphonates with rates among persons receiving other osteoporosis medications (e.g., raloxifene or calcitonin) and with Surveillance, Epidemiology, and End Results (SEER) estimates.[1] We searched the health care utilization records of Medicare beneficiaries who were beginning treatment with an oral bisphosphonate or other osteoporosis medications in order to find a new diagnosis of esophageal cancer and treatments for esophageal cancer (i.e., chemotherapy, radiation therapy, or surgical procedures).

The rates of esophageal cancer are shown in Table 1. In standardized analyses, we found no increase in the incidence rate of esophageal cancer among persons who received oral bisphosphonates as compared with persons who received other osteoporosis medications and as compared

Table 1. Incidence Rates and Incidence-Rate Ratios for Esophageal Cancer.*

Group	Incidence Rate per 100,000 Persons	Incidence-Rate Ratio (95% CI)
Persons receiving oral bisphosphonates	26.7	—
Persons receiving other osteoporosis medications	48.4	0.55 (0.06–4.72)
Persons in the SEER registry	23.7	1.12 (0.26–4.84)

* Surveillance, Epidemiology, and End Results (SEER) results are for 5-year age strata in men and women 65 years of age or older. Incidence-rate ratios are for the comparison of persons who received oral bisphosphonates with persons who received other osteoporosis medications (raloxifene or calcitonin) and those in the SEER registry; thus, ratios below 1.00 indicate a reduced risk among persons who received oral bisphosphonates. CI denotes confidence interval.

with SEER estimates. The rarity of esophageal cancer led to wide confidence intervals. However, the 95% confidence interval around the comparison with SEER incidence rates rules out a rate greater than 114.9 per 100,000 persons.

Daniel H. Solomon, M.D., M.P.H.
Amanda Patrick, M.Sc.
M. Alan Brookhart, Ph.D.
Brigham and Women's Hospital
Boston, MA 02115
dhsolomon@partners.org

Drs. Solomon and Brookhart report receiving grant support from Amgen. No other potential conflict of interest relevant to this letter was reported.

1. Ries LAG, Melbert D, Krapcho M, et al. SEER cancer statistics review, 1975-2005. Bethesda, MD: National Cancer Institute. (Accessed March 24, 2009, at http://seer.cancer.gov/csr/1975_2005/.)

TO THE EDITOR: With regard to Wysowski's letter: the time from exposure to oral bisphosphonates to the diagnosis of esophageal cancer was brief, with a mean duration of 1 to 2 years, and for this reason we doubt that bisphosphonate use was the cause of esophageal adenocarcinoma. Rather, we suspect that in light of the high incidence of coexisting osteoporosis and Barrett's esophagus among postmenopausal women, most women with esophageal adenocarcinoma had preexisting, but undiagnosed, Barrett's esophagus with dysplasia.

Lorenz C. Hofbauer, M.D.
Stephan Miehlke, M.D.
Dresden Technical University Medical Center
D-01307 Dresden, Germany
lorenz.hofbauer@uniklinikum-dresden.de

TO THE EDITOR: With regard to the letter by Wysowski: we suggest that the time between exposure to bisphosphonates and the diagnosis of esophageal cancer was too short to be compatible with a cause-and-effect relationship. Exposure to carcinogenic agents is measured in years before the development of a neoplasm. After it develops, a tumor may not be detected for years; for example, a tumor requires 30 volume doublings to reach 1 cm in diameter. Wysowski reports a time from exposure to diagnosis of 1.3 to 2.1 years. This duration results in a doubling time (16 to 26 days) that is incompatible with the natural history of esophageal cancer. Also, the author did not control for risk factors and did not assess the entire population at risk. Given the small number of cases reported, it is conceivable that the widespread use of bisphosphonates could even have a protective value.

H. Ian Robins, M.D., Ph.D.
Kyle D. Holen, M.D.
University of Wisconsin Paul P. Carbone Comprehensive Cancer Center
Madison, WI 53792

TO THE EDITOR: The usefulness of Wysowski's data is limited by the lack of a comparison group. Millions of people take bisphosphonates. Worldwide, esophageal cancer ranks fifth in the causes of death from cancer.[1] By chance, some people with cancer will be bisphosphonate users. Are 23 cases of cancer over a period of 13 years more than would be expected? Without controls, it is impossible to know.

Also, the data source is a voluntary-reporting database in which clinicians can report drugs as being a suspected cause of illness. Alendronate has long been known to cause esophagitis.[2] Clinicians observing esophageal cancer with bisphosphonate use might report it solely because of previous knowledge of this association with

esophagitis, resulting in a spurious association with cancer.

Nicholas J. Shaheen, M.D., M.P.H.
University of North Carolina School of Medicine
Chapel Hill, NC 27599-7080

1. The global burden of disease: 2004 update. Geneva: World Health Organization, 2008. (Accessed April 2, 2009, at http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf.)
2. de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996;335:1016-21.

TO THE EDITOR: Wysowski provides no information on the expected rates of esophageal cancer among patients in the age group she studied, and she provides no data on known risk factors, except for Barrett's esophagus in one patient. The prevalence of chronic gastroesophageal reflux disease, a risk factor for esophageal cancer, is not known. Clearly, one cannot conclude on the basis of Wysowski's letter that bisphosphonate use is associated with esophageal cancer.

Ethel S. Siris, M.D.
Martin W. Oster, M.D.
John P. Bilezikian, M.D.
Columbia University Medical Center
New York, NY 10032
es27@columbia.edu

Dr. Siris reports receiving consulting fees from the Alliance for Better Bone Health, Amgen, Eli Lilly, and Novartis and speaking fees from the Alliance for Better Bone Health, Eli Lilly, and Novartis; and Dr. Bilezikian, receiving consulting fees from the Alliance for Better Bone Health, Eli Lilly, GlaxoSmithKline, NPS Pharmaceuticals, and Novartis, investigator fees from NPS Pharmaceuticals, and speaking fees from the Alliance for Better Bone Health, Eli Lilly, and Novartis. No other potential conflict of interest relevant to this letter was reported.

THE AUTHOR REPLIES: The reports of esophageal cancer in users of oral bisphosphonates were voluntarily submitted to the FDA's Adverse Event Reporting System, an early-warning system for reporting suspected drug reactions. A major limitation of this system is underreporting; the extent of reporting is variable, but it is usually only about 5 to 15%.[1] Consequently, reliable incidence rates of esophageal cancer among users of oral bisphosphonates cannot be calculated from these reports and compared with U.S. cancer rates or those obtained from other sources.

Oral bisphosphonates might plausibly be associated with esophageal cancer, since they can cause erosive esophagitis,[2] delayed healing, and persistent mucosal abnormalities.[3] Multinucleated giant cells have been detected in esophageal inflammatory exudates.[2] Whether these or other cells undergo malignant transformation is not known at this time, although Singh and Odze have suggested that changes in multinucleated giant cells in esophagitis "probably represent a regenerative response to injury."[4]

Several correspondents state that the short duration of use of the drugs made the association improbable. However, not all patients' use was short term, and if patients were at increased risk before bisphosphonate use, a long duration of exposure might not be required. Alternatively, short-term use of an oral bisphosphonate could lead to detection of a preexisting tumor.

Although there is uncertainty about whether the use of oral bisphosphonates increases the risk of esophageal cancer, it seemed prudent to disclose the reports, advise against the use of these drugs in patients with Barrett's esophagus, and recommend definitive studies. Such studies should include a control group and be of sufficient size, with a sufficient duration of exposure and follow-up and with analyses of confounding variables. Although the study by Abrahamsen et al. incorporated some of these criteria, insufficient data on long-term exposure and the lack of information on smoking status, alcohol use or nonuse, and body-mass index are limitations. The study by Solomon et al. cannot be properly judged because it does not provide enough information on the control medications, exposure duration, standardization methods, and other issues.

Although my letter advises that oral bisphosphonates not be used in patients with Barrett's esophagus, there are insufficient data at this time to recommend screening asymptomatic patients for Barrett's esophagus before the initiation of therapy with oral bisphosphonates.

Finally, in considering the risks and benefits of therapy for osteoporosis, I note that a recent review article concluded that the efficacy of oral bisphosphonates in reducing nonvertebral and hip fractures in high-risk elderly women (≥75 years) has not been demonstrated.[5]

Diane K. Wysowski, Ph.D.
Food and Drug Administration
Silver Spring, MD 20993
diane.wysowski@fda.hhs.gov

The views expressed are those of the author and do not necessarily represent the official position of the Food and Drug Administration.

1. McAdams M, Staffa J, Dal Pan G. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. Pharmacoepidemiol Drug Saf 2008;17:229-39.
2. Abraham SC, Cruz-Correa M, Lee LA, Yardley JH, Wu T-T. Alendronate-associated esophageal injury: pathologic and endoscopic features. Mod Pathol 1999;12:1152-7.
3. Ribeiro A, DeVault KR, Wolfe JT III, Stark ME. Alendronate-associated esophagitis: endoscopic and pathologic features. Gastrointest Endosc 1998;47:525-8.
4. Singh SP, Odze RD. Multinucleated epithelial giant cell changes in esophagitis: a clinicopathologic study of 14 cases. Am J Surg Pathol 1998;22:93-9.
5. Inderjeeth CA, Foo AC, Lui MM, Glendenning P. Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: review of the evidence. Bone 2008 December 16 (Epub ahead of print).

Mutations in a Thiamine-Transporter Gene and Wernicke's-like Encephalopathy

TO THE EDITOR: We report on two previously healthy Japanese brothers with a newly discovered recessively inherited syndrome similar to Wernicke's encephalopathy that developed in the second decade of life; this syndrome was manifested clinically as thiamine-responsive diplopia and ptosis without serum thiamine deficiency. The patients had complex partial seizures resulting in status epilepticus. The administration of high-dose thiamine (up to 600 mg) improved the seizures within 24 hours, although the ophthalmoplegia, nystagmus, and ataxia continued for several weeks. There were no extrapyramidal features. Magnetic resonance imaging (MRI) of the brain showed high-intensity signals in the bilateral medial thalamus and periaqueductal region on fluid-attenuated inversion recovery images (Fig. 1A); these signals were characteristic of findings in Wernicke's encephalopathy and became normal within 1 month after treatment. Interviews of the patients' relatives confirmed that there was no consanguinity in their parents. Subacute ophthalmoplegia with nystagmus and ataxia occurred repeatedly within several months after the discontinuation of 100 mg of thiamine per day. There was no history of chronic alcoholism in either patient. Korsakoff's psychosis did not occur even after long periods of Wernicke's-like symptoms.

The clinical and imaging features resembling Wernicke's encephalopathy in these patients suggested that the syndrome was caused by a genetic disorder of thiamine metabolism.[1] Genomic analysis of *SLC19A3* encoding human thiamine transporter 2 (hTHTR2)[2,3] revealed that the patients were compound heterozygotes for the K44E and E320Q mutations; these mutations were not present among 192 ethnically matched control subjects (Fig. 1B and 1C). Gene-expression analyses of mammalian culture cells showed the majority of the K44E mutant to be impaired in intracellular transport while remaining normal in the endoplasmic reticulum. The E320Q mutant was identical in cell-surface localization to the wild-type protein (Fig. 1D), whereas intracellular thiamine uptake activity was decreased significantly (Fig. 1E). High expression of *SLC19A3* RNA in the thalamus (Fig. 1F) may explain the selective thalamic lesions on MRI.

Mutation of *SLC19A3* causes a biotin-responsive basal-ganglia disease characterized by subacute encephalopathy with rigidity and dystonia. Biotin is effective and thiamine is ineffective in treating this childhood-onset disease.[4,5] The features of this process on MRI are bilateral necrotic lesions in the caudate heads; this is markedly different from the locus of lesions in the disease we describe.[4] The absence of serum thiamine deficiency and the efficacy of high-dose thiamine in our patients suggest that dysfunction of hTHTR2 may induce the expression of another human thiamine transporter 1–encoded gene called *SLC19A2*, thereby increasing intracellular thiamine transport in enterocytes and neuronal cells. The identification of this syndrome provides insight into the thiamine metabolism associated with Wernicke's encephalopathy in humans and suggests that the mechanism of Korsakoff's psychosis may be independent of these thiamine pathways.

Satoshi Kono, M.D., Ph.D.
Hiroaki Miyajima, M.D., Ph.D.
Kenichi Yoshida, M.D., Ph.D.
Akashi Togawa, M.D., Ph.D.
Kentaro Shirakawa, M.D.
Hitoshi Suzuki, M.D.

Hamamatsu University School of Medicine
Hamamatsu 431-3192, Japan
satokono@hama-med.ac.jp