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From Medscape Medical News About Face: Oral Bisphosphonates Linked to Esophageal Cancer



Nick Mulcahy

September 3, 2010 — In an about face of findings, a new study reports that oral bisphosphonates — widely prescribed for osteoporosis — are associated with an increased risk for esophageal cancer. The study comes just weeks after another study, using the same database, found no such link.

The new case-control study found that the risk was statistically significant among patients who had 10 or more prescriptions for the drugs — compared with patients who had 1 to 9 prescriptions.

The relative risk also increases with duration of use; it doubles over about a 5-year period, according to the authors of the new study, led by Jane Green, PhD, a clinical epidemiologist from the Cancer Epidemiology Unit at the University of Oxford in the United Kingdom.

However, an expert in gastroesophageal cancer contacted by *Medscape Medical News* suggested that clinicians should not stop prescribing oral bisphosphonates.

Clinicians need to weigh the benefits of oral bisphosphonates such as the reduction in hip fracture against the risks such as the increase in esophageal cancer, said Gerard Blobe, MD, associate professor of medicine at Duke University School of Medicine in Durham, North Carolina.

"The absolute risk increase found in the study is still pretty small — 1 in 1000 to 2 in 1000 with about 5 years of use of oral bisphosphonates," he observed about the new data.

"I would say that, generally, the benefits outweigh the risks," he said.

Dr. Blobe also explained that oral bisphosphonates could theoretically increase esophageal cancer because "irritation" of the esophagus might "set the stage for cancer in some patients."

The new study's findings on oral bisphosphonates conflict with a [recent British study](#) that found no link.

Notably, both studies used the UK General Practice Research Database.

"What would cause these differences [in findings]?" asks an editorial that accompanies the new study, both of which were published online September 2 in *BMJ*.

A "major difference" in the 2 studies is the average length of follow-up, notes the editorialist, Diane Wysowski, PhD, an epidemiologist at the US Food and Drug Administration (FDA) in Silver Spring, Maryland. The earlier negative study

had 4.5 years of follow-up; the new positive study has 7.5 years.

The positive study also had "an adequate sample size," said Dr. Wysowski.

Dr. Green and her coauthors said that their positive study had "greater statistical power" than the negative study — with 5 matched controls per case, compared with equal numbers in the exposed and comparison groups in negative study.

Even if oral bisphosphonates cause cancer, "the incidence of esophageal cancer in this population of users would be expected to remain relatively low," writes Dr. Wysowski.

Despite this comment, another gastroenterologist from Duke said that esophageal cancer is of growing concern in the United States and other industrialized countries.

"The incidence of esophageal adenocarcinoma is rising more rapidly than any other malignancy in the past 5 years in Western countries. The reasons are unknown," said Ivy Altomare MD, assistant professor of medicine and a colleague of Dr. Blobe.

Advice to Patients

The immediate question for clinicians is what to tell patients, says Dr. Wysowski. Her primary recommendation is to tell patients to take the pills correctly. Dr. Blobe explained the reason for the recommendation.

As soon as it was recognized that oral bisphosphonates were associated with esophageal problems, the package inserts for these drugs were changed, he said. The change included directions on how to best take the drugs, and dictated that patients with a history of esophageal problems not be prescribed these agents.

After the package insert was changed, "the incidence of esophageal-related problems with the drugs subsequently dropped," he said. This chain of events suggests that noncompliant patients must be the ones who develop problems, he said.

Dr. Wysowski reminds clinicians to reinforce directions for drug usage with each prescription. Namely, remind patients to take oral bisphosphonates in the morning with a full glass of plain water on an empty stomach — at least 30 to 60 minutes before the first food, beverage, or medication.

Also tell patients not to recline for at least 30 to 60 minutes after taking an oral bisphosphonate.

The new study results might be, in an odd way, useful to clinicians, suggested Dr. Blobe. "This result could incentivize patients to take the pill correctly," he said.

Study Results

The 2 studies come out about a year and a half after the FDA reported 23 cases of esophageal cancer between 1995 and 2008 in patients using alendronate and another 31 cases in patients using a variety of bisphosphonates in Europe and Japan.

Dr. Wysowski was the author of that FDA report, which was published in January 2009 (*N Engl J Med.* 2009;360:89-90). That paper immediately prompted a couple of quick studies. However, those 2 studies had methods and data that were "sparse", notes Dr. Wysowski in her current editorial.

So that leaves the new positive study and the earlier negative study as the main objects of attention in the debate this matter.

The 2 sets of investigators studied the problem in slightly different ways, points out Dr. Wysowski.

The negative study compared the incidence of esophageal cancer and gastric cancer in patients who were exposed or not exposed to oral bisphosphonates, and found no increase in the risk for either cancer. The positive study compared the frequency of oral bisphosphonate exposure in cases and matched noncases.

In their positive study, Dr. Green and her colleagues set out to test the hypothesis that risk for esophageal, but not gastric or colorectal, cancer is higher in users of oral bisphosphonates.

They used a UK General Practice Research Database cohort and identified men and women 40 years or older who were diagnosed from 1995 to 2005 — 2954 with esophageal cancer, 2018 with gastric cancer, and 10,641 with colorectal cancer. Five controls per case were matched for age, sex, general practice, and observation time.

After adjustment for smoking, alcohol, and body mass index, they examined the relative risks for the 3 different cancers.

They found that the incidence of esophageal cancer was higher in cases with 1 or more previous prescriptions for oral bisphosphonates than in those with no such prescriptions (relative risk [RR], 1.30; 95% confidence interval [CI], 1.02 - 1.66; $P = .02$).

As noted above, the risk for esophageal cancer was significantly higher after 10 or more prescriptions (RR, 1.93; 95% CI, 1.37 - 2.70) than after 1 to 9 (RR, 0.93; 95% CI, 0.66 - 1.31; P for heterogeneity = .002), and for use for more than 3 years (RR vs no prescription, 2.24; 95% CI, 1.47 - 3.43).

This doubling of risk in longer-term users (ie, over 3 years; the average length of use was about 5 years) is where most of the risk is with bisphosphonates, according to the data. The relative risks for people who used oral bisphosphonates for less than a year or for 1 to 3 years were about 1 for both — in other words, they had no increased risk.

Cancers of the stomach and colorectum were not associated with oral bisphosphonates, the authors reported.

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