PPIs Raise Risk of Some Fractures, but Not Hip

BY MARY ANN MOON

FROM THE ARCHIVES OF INTERNAL MEDICINE

The use of proton pump inhibitors does not appear to raise the risk of hip fracture in postmenopausal women but may raise the risk of spine, forearm, wrist, and total fractures modestly.

Several large epidemiologic studies have suggested that PPI use may be associated with an increased risk for osteoporotic fractures, but other studies have found no such link. Shelly L. Gray, Pharm.D., and her associates examined the issue using data from the Women's Health Initiative, a large study of an ethnically diverse cohort of postmenopausal women followed at 40 U.S. medical centers for a mean of 7.8 years.

For this analysis, data on 161,806 women aged 50-79 years were included. A total of 3,396 (2%) of these study subjects were taking omeprazole or lansoprazole at baseline.

Women who took PPIs were more likely than those who did not to have osteoporosis or a history of fractures, obesity, treated diabetes, or a history of several health conditions; to take other medications chronically; and to have poorer self-reported health and physical function. "We did our best to adjust for these baseline differences, but, like all observational studies, residual or unmeasured confounding could explain increased associations for some fracture types," said Dr. Gray of the University of Washington School of Pharmacy, Seattle, and her colleagues.

During more than a million person-years of follow-up, there were 1,500 hip fractures, 4,881 forearm or wrist fractures, 2,315 clinical spine fractures, and 21,247 total fractures.

PPI use was not related to hip fracture risk. There also was no association between hip fracture risk and longer duration of PPI use.

After the data were adjusted to account for possible confounding factors, PPI use was not related to hip fracture risk. There also was no association between hip fracture risk and longer duration of PPI use, Dr. Gray and her associates reported (Arch. Intern. Med. 2010;170:765-71).

In addition, there were no differences between women who used PPIs and women who didn't in the change in bone mineral density over time. Similarly, there was no consistent relationship between duration of PPI use and risk of any fracture.

However, the drugs raised the relative risk of clinical spine fracture by 47% (hazard ratio, 1.47); the relative risk of forearm or wrist fracture by 26% (HR, 1.26); and the relative risk of total fractures by 25% (HR, 1.25).

Although these findings leave many questions unresolved, "based on the accumulation of evidence, it is prudent for clinicians to periodically reevaluate the need for long-term PPI therapy," the investigators said.

For older patients who do require the treatment, "it is reasonable to focus on using the lowest effective dose, ensuring adequate dietary calcium intake, and adding calcium supplements when necessary," they added.

In an editorial comment accompanying this report, Dr. Mitchell H. Katz of the San Francisco Department of Public Health characterized the increases in nonhip fractures as "modest" but said that PPIs are so widely used that those modest increases "add up to a lot of morbidity on a population level" (Arch. Intern. Med. 2010;170:747-8).

"We should offer treatments other than PPIs for functional dyspepsia, prescribe short courses of PPI treatment (after disclosure of possible risks and benefits), and consider a trial of discontinuing PPI therapy in patients who are asymptomatic.

"Once our patients fully appreciate the adverse effects of PPIs, they themselves may prefer other treatments, including tincture of time"; behavioral changes such as eating smaller meals, losing weight, quitting smoking, and reducing stress; and nonmedical interventions such as raising the head of the bed, Dr. Katz said.

The WHI Program was funded by the National Heart, Lung, and Blood Institute.

Dr. Gray reported no financial conflicts of interest. Her associate, Andrea Z. LaCroix, Ph.D., reported ties to Pfizer Inc., Procter & Gamble Co., and Sanofi-Aventis. Dr. Katz is an independent consultant for Health Management Associates. ■

Therapeutic Retinoids Do Not Raise Risk of Fracture

BY MARY ANN MOON

FROM ARCHIVES OF DERMATOLOGY

Treatment with vitamin A analogues such as isotretinoin and acitretin does not increase fracture risk, according to findings from a nationwide Danish case-control study.

Of all fractures sustained in a single year, no form of systemic or topical vitamin A analogues was associated with fracture risk at any skeletal site, said Dr. Peter Vestergaard and his associates at Aarhus (Denmark) University Hospital.

Previous research has yielded conflicting results. Some studies have found that high-dose therapy is related to an increased risk of fracture and adverse bone changes, including hyperostosis, hypercalcemia, impaired bone turnover, and decreased bone mineral density, while other studies have found no such association.

The results of this large population-based study show that "even very large daily doses of 14 mg of vitamin A analogues (equivalent to 14,000 micrograms of retinol equivalents per day) were not associated with an increased risk of fractures. It thus seems that vitamin A analogues are safe in terms of fractures, even at very high doses," Dr. Vestergaard and his colleagues wrote (Arch. Dermatol. 2010;146:478-82).

They used data from 124,655 cases of fracture that occurred in 2000 and 373,962 control cases matched for age and sex. The data were adjusted to account for the severity of the underlying disease requiring treatment with vitamin A analogues, as well as for the concomitant use of drugs known to affect fracture risk, such as corticosteroids and antiepileptic agents.

There was no association between any form of vitamin A analogue and fracture risk at any site. Moreover, no trend was found between increasing dose or increasing duration of treatment and any fracture risk, the investigators reported.

There also was no association with fracture risk when the use of individual vitamin A analogues was analyzed.

"Even though some studies have reported a decreased BMD with high doses of vitamin A as retinol in dietary intake or as supplements, the decrease may not have been of such magnitude that it altered bone biomechanical competence," Dr. Vestergaard and his associates noted.

In an editorial accompanying the report, Dr. John J. DiGiovanna of Brown University, Providence, noted that these results are particularly reassuring because the investigators examined "a large population of humans treated under real therapeutic conditions" and because the end point (fracture) was clinically important.

The main weakness of the study was that it could not completely account for potentially confounding factors such as smoking habits, body mass index, vitamin D status, and sun exposure, he wrote (Arch. Dermatol. 2010; 146:551-3).

"While it is reassuring to see this evidence of retinoid drug safety in relation to bone demineralization in a large population, the treatment of patients must rely on personalized prescription. Sound measures for good skeletal health, including adequate nutrition (especially vitamin D and calcium, etc.) and healthy physical activity, should be encouraged.

"Monitoring may be indicated for individuals with a family or personal history of osteoporosis, advanced age, and exposure to agents known to cause demineralization, and possibly those requiring long-term or high-dose retinoid drug therapy," Dr. DiGiovanna added.

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