

# High-Dose Vitamin D May Raise Fracture Risk

BY MARY ANN MOON

FROM JAMA

Far from protecting older women from falls and fractures, once-yearly high-dose oral vitamin D raised the risk of falls by 15% and that of fractures by 26%, according to researchers in Australia.

These risks were highest in the 3-month period immediately after each annual dose, said Kerrie M. Sanders, Ph.D., of the University of Melbourne and her associates.

As this study used the “largest total annual dose of vitamin D (500,000 IU) reported in any large randomized controlled trial,” it is possible that these adverse outcomes are related to the dosage, or perhaps to the once-a-year regimen. But the levels of 25-hydroxycholecalciferol achieved in these subjects can also occur with other dosing regimens, so it appears that the safety of all high-dose vitamin D supplementation warrants further examination, they noted.

Dr. Sanders and her colleagues performed their single-center study in 2,256 white women aged 70 and older. They were considered at risk for hip fracture because of their family or personal histories or because they reported recent falls.

The subjects were randomly assigned to receive a single oral dose of vitamin D (cholecalciferol) or a matching placebo at the same time every year for 3-5 years. Lab studies in a subgroup of the subjects showed that the active treatment raised levels of 25-hydroxycholecalciferol an average of 41%, as expected.

There were 5,404 falls during follow-up, involving 74% of the women taking vitamin D and 68% of those taking placebo. The rate of falls was 83 per 100 person-years with vitamin D, compared with 73 per 100 person-years



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with placebo, a statistically significant difference.

The increase in falls with active treatment was noted in falls that produced fractures, falls that did not produce fractures, and falls that produced soft-tissue injury. The percentage of falls requiring a physician's visit was similar between the two groups of subjects, at approximately 27% in both.

A total of 155 women taking vitamin D sustained 171 fractures during follow-up, compared with 125 women taking placebo who sustained 135 fractures. This translates to a rate of 4.9 fractures per 100 person-years with active treatment and 3.9 fractures per 100 person-years with placebo. These risks of falls and of fractures did not change after the data were adjusted to account for subjects' calcium intake.

“Contrary to our hypothesis, participants receiving annual high-dose oral cholecalciferol experienced 15% more falls and 26% more fractures than [did] the placebo-

bo group. Women not only experienced excess fractures after more frequent falls but also experienced more fractures that were not associated with a fall,” the investigators noted (JAMA 2010;303:1815-22).

“A post hoc analysis found that the increased likelihood of falls in the vitamin D group was exacerbated in the 3-month period immediately following the annual dose, and a similar temporal trend was observed for fractures,” they added.

The reason for these counterproductive effects is not yet known, but it is possible that the once-a-year oral regimen—compared with either a regimen that divides the oral doses or one that uses intramuscular doses—is at fault. “It is reasonable to speculate that high serum levels of vitamin D or metabolites resulting from the large annual dose, subsequent decrease in the levels, or both might be causal,” Dr. Sanders and her associates wrote.

In an accompanying editorial, Dr. Bess Dawson-Hughes and Susan S. Harris, D.Sc., of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, said that these study findings should not detract from the importance of “correcting widespread vitamin D deficiency and insufficiency.

“There is no evidence for adverse effects of more frequent, lower-dose regimens, so daily, weekly, or monthly dosing with vitamin D<sub>3</sub> appears to be the best option for clinicians at this time,” they noted (JAMA 2010; 303:1861-2).

**Disclosures:** This study was supported by the National Health and Medical Research Council and the Australian Government Department of Health and Ageing. No conflicts of interest were reported by Dr. Sanders and her associates, Dr. Dawson-Hughes, or Dr. Harris.

## Topical NSAIDs Safe in Elderly Osteoarthritis Patients

BY SHERRY BOSCHERT

FROM THE ANNUAL MEETING OF THE AMERICAN MEDICAL DIRECTORS ASSOCIATION

LONG BEACH, CALIF. — A higher rate of adverse events in older patients with knee osteoarthritis treated topically for 12 weeks with an NSAID, compared with placebo, was caused mainly by application-site reactions but included one serious cardiovascular event that might have been related to the drug treatment, a post hoc analysis of data on 538 patients found.

The investigators analyzed data on people aged 65 years and older with symptomatic knee osteoarthritis (433 had comorbid hypertension, diabetes, or cardiovascular disease). Their source was three larger randomized, double-blind trials—two unpublished—that had looked at broader populations. Patients applied 4 g/day of either diclofenac sodium 1% gel (Voltaren) or the drug's vehicle to one painful knee.

One 80-year-old woman with hypertension and diabetes, among the 274 patients on diclofenac sodium 1% gel, developed deep vein thrombosis and pulmonary embolism that possibly was related to treatment, Dr. H. Richard Barthel and his associates reported in a poster presentation.

Overall, 56% of patients on diclofenac gel developed adverse events, compared with 44% of 264 patients treated with placebo gel, added Dr. Barthel, a

rheumatologist in Santa Barbara, Calif.

NSAIDs are known to increase risk for cardiovascular or renal problems in a dose-related fashion, especially in older patients and people with hypertension, diabetes, or cardiovascular disease. Topical formulations may reduce this risk by reducing systemic exposure to NSAIDs compared with oral formulations. The ad hoc analysis compared the gel only to placebo, not to oral therapy, and found higher rates of adverse events for the drug vs. placebo.

Application-site reactions occurred in 8.8% on diclofenac gel and 1.1% on placebo. Serious adverse events occurred in 2.6% on diclofenac and 1.1% on placebo. Adverse cardiovascular events were seen in 2.6% on diclofenac and 1.1% on placebo. Adverse renal events were seen in 1.1% on diclofenac and 0.4% on placebo.

Among more common adverse events, 11% of subjects on diclofenac and 10% on placebo reported headache, 8% on diclofenac and 7% on placebo reported arthralgia, and 8% on diclofenac and 6% on placebo reported back pain.

The analysis included 307 patients with hypertension, 84 with diabetes, and 42 with cardiovascular disease. In the hypertension subgroup, adverse events were seen in 54% of 159 people randomized to diclofenac gel, compared with 45% of 148 people using placebo. In the diabetes subgroup, adverse events occurred in 19 (51%) of 37 patients treated with diclofenac and in 21 (48%) of 47 treated with placebo. In the subgroup

with cardiovascular disease, adverse events occurred in 15 (56%) of 27 on diclofenac and in 2 (13%) of 15 on placebo, though none developed an adverse cardiovascular event.

**Disclosures:** Dr. Barthel conducted the study under a research contract for Novartis, which makes Voltaren. His associates in the study were employees of Novartis or of Endo Pharmaceuticals, which markets the drug.

### Topical Gel Will Change OA Therapy

The therapy of osteoarthritis remains insufficient in many patients. It is particularly problematic in the elderly where there are often comorbid diseases that limit our options for several of the oral medications, particularly NSAIDs and potent analgesics. The recent Food and Drug Administration approval of diclofenac has changed the therapeutic paradigm. Diclofenac gel 1% has been approved for osteoarthritis of the knee, hand, and other superficial joints, and Pennsaid has been approved for osteoarthritis of the knee.

In this posthoc pooled analysis of 538 patients over 65 years of age treated for 3 months with the diclofenac gel 1% for osteoarthritis of the knee, we see an increase in irritation at the site of application, but a minimal increase in adverse events involving blood pressure, renal func-

tion, hepatic dysfunction, and gastrointestinal ulcer disease. Pharmacokinetic studies have shown that systemic absorption of the topical diclofenac is 40 times less than oral diclofenac. This improved safety allows us to provide therapy to patients otherwise unable to receive anti-inflammatory drugs.

It will be no surprise if the guidelines for therapy of osteoarthritis from the United States will soon approximate those from Europe, where topical NSAIDs are part of the therapeutic algorithm for osteoarthritis.

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