EDITOR'S CHOICE

Case control study

Older women who use bisphosphonate for longer than 5 years may have increased odds of a subtrochanteric or femoral shaft fracture, but absolute risk is low

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Commentary on: **Park-Wyllie LY**, Mamdani MM, Juurlink DN, *et al.* Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA* 2011;**305**:783–9.

Context

It is now recognised that fractures of the subtrochanteric femur or femoral shaft (ST/FS fractures) can be divided radiologically into (1) typical fractures and (2) atypical fractures. The latter appear to be rare in patients untreated by bisphosphonates. In this new study, Park-Wyllie *et al* used Ontario claims data to investigate the association between the amount of bisphosphonates taken and the risk of ST/FS fractures.

Methods

The study was a nested 5:1 case-control study, linking prescriptions with hospitalisations, physician service claims and death certificates. Women aged 68 years or older who filled prescriptions for bisphosphonates at least once over a 6-year period were included. Those with malignant disease in the past 10 years, specific bone diseases or secondary causes of osteoporosis (past 5 years) and osteoporosis treatment in the past year were excluded, providing 205 466 women for study.

Cases were defined as first ST/FS fracture, excluding fractures treated exclusively with hip replacement and fractures due to vehicle accidents and falls from a height. In a secondary analysis, cases were defined as those with a classic osteoporotic fracture (femoral neck or intertrochanteric hip, FN/IT). Another secondary analysis focused on long-term users of bisphosphonates.

Bisphosphonate exposure was categorised as long-term use (≥5 years), intermediate use (between 3 and 5 years), short-term use (100 days to 3 years) and a reference category for 'transient use' (<100 days).

Analysis was conditional logistic regression with adjustment for socioeconomic status (by postcode), key other medications, count of medications, comorbidities, physician claims and existence of a bone mineral measurement.

Findings

In 716 patients with new ST/FS fractures, bisphosphonate exposure was transient in 5.9%, short term in 48.7%, intermediate in 28.5% and long term in 16.9%. In 3580 bisphosphonate-treated controls who did not sustain such fractures, exposure was transient in 6.1%, short term in 51.2%, intermediate in 29.9% and long term in 12.9%. Logistic regression analysis found no increased risk in the short term and intermediate exposure categories, but increased risk in the long-term exposed category with an adjusted OR of 2.74 (95% CI 1.25 to 6.02). In patients treated for more than 5 years, 64% of such fractures could statistically be explained by long-term use. Approximately one in ten ST/FS fractures in users could be avoided if no patient was treated for more than 5 years. For FN/IT fractures – classic osteoporotic fracture sites where bisphosphonates are known to reduce risk – the adjusted OR for long-term use of bisphosphonates was 0.76 (95% CI 0.63 to 0.93).

Commentary

Including all ST/FS fractures as the condition of interest in this study means that risks of their occurrence that were identified mark an upper boundary because these fractures include both atypical and osteoporotic fractures. A gradient in risk could suggest a causal relationship. If patients with long-term exposure to bisphosphonates are more likely to fracture then bisphosphonates could be the culprit. But like any association, dose-response relationships can be spurious. For example, patients who take bisphosphonates for a long period of time may do so because they have unusually strong risk factors for fracture. Patients who adhere faithfully to bisphosphonates may also adhere to other medications that could predispose them to fractures. Glucocorticoids and proton pump inhibitors (PPI) were used by a large proportion of patients in this study and in case reports of radiologically adjudicated atypical fractures. PPIs have been linked to increased fracture risk[1] and to attenuation of the effect of alendronate.[2] The findings here were adjusted for baseline PPI and glucocorticoid use, though entering these covariates in a time-dependent Cox proportional hazards analysis might be more informative. Bisphosphonates cause dyspepsia so many patients using PPIs might not have done so at baseline.

The design of this study, a nested case-control study, did not allow calculation of absolute risks and appraisal of competing risks (eg, death) that could have been calculated as information from the full cohort was available. Also, there were large differences between cases and controls. For example, 70% of cases had prior fractures, 67% were 'fallers', and 45% used PPIs; among controls, proportions with these characteristics were 24%, 6% and 36%, respectively. Unmeasured confounders may have been similarly unbalanced. One may compare the known effects of bisphosphonates on hip fractures with data from the current study. Interestingly, although 3 years of treatment in clinical trials reduced the risk of hip fracture by 40–50% in conservative intention-to-treat analyses,[3 4] the current study reports a risk reduction of only 14% after 3–5 years. Some patients in the current study would

not have been eligible for participation in trials due to concomitant diseases, but the discrepancy in risk reduction raises questions about the current analysis that are worthy of further study. Observational studies may not reproduce effects observed in clinical trials. For example, US claims data[5] showed no difference in the risk of ST/FS fractures between bisphosphonate users and patients treated for osteoporosis with weaker antiresorptive drugs not believed to carry a risk of atypical femur fractures.

Atypical femur fractures are too rare for reliable risk information to be drawn from randomised controlled trials (RCTs); the study by Park-Wyllie *et al* provides new information on the upper boundary of risk seen in patients who have received prolonged treatment.

Competing interests BA has received grant or research support from Novartis, Nycomed, Amgen. He is also on the Speakers Bureau with Nycomed, Merck, Eli Lilly.

References

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