THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Bisphosphonates:
Do they prevent or cause bone fractures?

Previous Therapeutics Letters have highlighted important high quality systematic reviews by other independent groups such as Prescrire (France) and the Cochrane Collaboration. This Letter presents the abstract and highlights of a review produced by an independent Spanish organization and published in the Drug and Therapeutics Bulletin of Navarre (BIT, vol. 17, nr. 4, Aug-Oct 2009). We encourage readers to read and comment on the full 23 page article in English or Spanish, which has been posted on our web site: www.ti.ubc.ca/letter78

Abstract

Objective: to describe the effects of bisphosphonates with respect to whether they prevent or cause bone fractures.

Methods: a review of the main short and long-term randomized clinical trials, long-term cohort studies and case reports of atypical fractures with bisphosphonates published in MEDLINE since 1965.

Results: the effect of treatment with bisphosphonates versus placebo for short and long-term studies is described in absolute terms for the incidence of vertebral, hip and "non-vertebral" fractures. In addition, the current evidence on atypical femur fractures associated with bisphosphonate use is summarized.

Conclusions: in the short-term, bisphosphonates show some effectiveness in preventing vertebral fractures demonstrated by x-ray. The efficacy with regard to preventing hip fractures is uncertain; for primary prevention hip fractures are not reduced and for secondary prevention the effect is of small magnitude and of questionable clinical relevance. In the long-term, there is an increased risk of atypical fractures affecting the subtrochanter and diaphysis of the femur. In addition, one cohort study suggests the incidence of hip fractures could be increased instead of reduced. Clarification of the long-term effects of bisphosphonates is therefore necessary and suspension of the use of these drugs for osteoporosis should be considered.

Highlights

Short-term evidence (1-3 years)

....The first most widely used drug was alendronate, which was approved by the FDA in September 1995

for the prevention and treatment of post-menopausal osteoporosis in relation to its capacity to increase bone density. Three years later risedronate was approved for the same indication….. When bisphosphonates came onto the market, they had demonstrated efficacy to improve the surrogate endpoint, bone density, but there was no evidence for reduction of bone fractures. They were introduced on the theoretical assumption that the increase in bone density implied strengthening of the bone, and therefore a reduction in the risk of fracture.

Vertebral fractures

Subsequently pivotal clinical trials were conducted where the primary outcome was not bone density, but rather the prevention of morphological vertebral fractures determined by radiology. This was initially defined as a 20% reduction of the height of any vertebra in the case of the studies with alendronate…. However, in the trials with risedronate the term "vertebral fracture" was arbitrarily re-defined, as a 15% reduction in the height of the vertebra, which led to an increase in the incidence of this outcome simply due to the change in criteria. Bisphosphonates did show efficacy in reducing these vertebral height ("fractures") with a reduction in absolute risk of between 1% and 8%. The absolute effect in reducing symptomatic events is much less given that only a third of people with radiologically demonstrated vertebral fractures have clinical symptoms....

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Alendronate

.....A meta-analysis first published in 2002 and updated as a Cochrane review in 2009 included clinical trials with a duration of more than one year. The outcomes were incidence of vertebral, non-vertebral, hip and wrist fractures. In this review a distinction was made between primary and secondary prevention of fractures. There was no proven effect on symptomatic fractures for primary prevention. For secondary prevention alendronate given for 3 years reduced the absolute risk of hip fractures by 0.7%, and non-vertebral fractures by 2.1%.....

Risedronate

The case of risedronate is similar to that of alendronate. ….. …in a Cochrane review there was no statistically significant reduction of symptomatic fractures for primary prevention. For secondary prevention risedronate given for 3 years reduced the absolute risk of hip fractures by 0.7%, and non-vertebral fractures by 2.1%....

Long-term evidence (more than 3 years)

In 2006, the FLEX trial was published. This consisted of a follow up period of one of the pivotal trials with alendronate (FIT). The women treated with alendronate for five years were randomly assigned to continue with the drug for another five years or receive placebo. No significant differences between treatment groups were observed for all clinical fractures, alendronate 21% and placebo 20%, RR 0.93 [0.71-1.21] or nonvertebral fractures, alendronate 19% and placebo 19%, RR 1.00 [0.76-1.32].....

Between 2006 and 2007 three papers were published on atypical fractures due to alendronate……During 2008 more cases of atypical fractures (diaphyseal and subtrochanteric) were published and the number of patients in the series increased (15, 17 and 70 individuals in the three last references cited). The association between the use of bisphosphonates and the appearance of fractures was finally becoming consolidated.

....During 2009 a well-designed case-control study was carried out to evaluate the association of low impact femur fractures and the long-term use of bisphosphonates. A comparison was made between 41 subtrochanteric or diaphyseal fractures with 82 control patients with femoral or intertrochanteric fractures. A strong association was found between the use of bisphosphonates and atypical fractures (OR = 4.4; 95%CI, 1.7-11.5).

.....The French journal La Revue Prescrire petitioned the European Medicines Agency to submit data available on atypical fractures related to alendronate. In response, the European Medicines Agency issued a public statement in February 2009 describing 115 reported cases of patients treated between 18 months and 10 years. Of these, 84 cases involved subtrochanteric fractures or affected the diaphysis. The majority occurred with no previous trauma and were preceded by pain for weeks or months…..

.....In 2008 a particularly relevant retrospective cohort study, in Danish women with no previous hip fracture was published. This 8-year study compared 5,187 women treated with alendronate and with at least one fracture at baseline with a control group of 10,374 women receiving no treatment matched for the same baseline fractures, age etc. Surprisingly, the women receiving alendronate were found to have a statistically significantly higher incidence of hip fracture 18.23 per 1,000 women-years as compared to the controls 11.86 per 1,000 women-years [HR = 1.50 (1.26-1.79)]).....

Conclusions

.....Given that bisphosphonates can cause severe adverse effects including fractures, which they are meant to prevent, it is urgent that the overall benefits and harms of long-term treatment be clarified. The available evidence suggests that the benefit-harm balance may be unfavourable for their use in osteoporosis.

Commentary

We found this Spanish review of bisphosphonates challenging and thought provoking and thus worthwhile sharing with our readers. **It has stimulated the TI to conduct a full systematic review and critical appraisal of this widely prescribed class of drugs.** This review will focus on longer term randomized controlled trials, observational studies, case control studies and case reports of serious adverse events. We will report our findings in a future Therapeutics Letter.

The full text of the Drug and Therapeutics Bulletin of Navarre article on bisphosphonates highlighted in this Therapeutics Letter, including the complete list of references, has been posted on our web site: www.ti.ubc.ca/letter78