THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

A Systematic Review of the Efficacy of Bisphosphonates

Therapeutics Letter #78 summarized the findings from a review by an independent Spanish bulletin under the title **"Bisphosphonates: Do they prevent or cause bone fractures?"** [1] In this Letter we report the findings of our own systematic review of the randomized controlled trial evidence of the benefits and harms of bisphosphonates.

Objective

To assess the clinical efficacy of alendronate (Fosamax®), etidronate (Didronel®, Didrocal®) and risedronate (Actonel®) for primary and secondary prevention of fractures in postmenopausal women.

Methods

Types of studies: Randomized controlled trials (RCTs) lasting at least one year.

Types of participants: Post-menopausal women without prior fractures or vertebral compression (primary prevention) or with prior fractures or vertebral compression (secondary prevention).

Types of interventions: alendronate, etidronate or risedronate at any dose, versus placebo or no bisphosphonate.

Types of outcomes: Total mortality, total serious adverse events, hip fracture, wrist fracture, withdrawals due to adverse effects, total withdrawals. We did not analyze or report any asymptomatic outcomes of questionable meaning to women, i.e. bone mineral density or radiographically defined vertebral compression (incorrectly referred to as a fracture).

Search Strategy: We searched Cochrane CENTRAL, MEDLINE and EMBASE for relevant RCTs published from January 1966 to October 2011.

Data Collection and Analysis: Study selection and data abstraction involved two independent reviewers. We conducted a meta-analysis to compare the incidence of outcomes between bisphosphonates and controls and presented the results as relative risks with 95% confidence intervals. We assessed risk of bias for each trial using the Cochrane risk of bias tool.

Results

We identified 33 RCTs that met the inclusion criteria for the review, comprising 25,735 women: 11,893 alendronate, 679 etidronate and 13,163 risedronate. Despite the relatively large number of RCTs and individuals

studied, several of the outcomes of interest were only reported in a minority of the RCTs. The two outcomes assessing benefit minus harm (total mortality and total serious adverse events) were reported in 33% and 84% of randomized patients, respectively. **Neither of these was affected by bisphosphonate therapy as compared to placebo: total mortality, RR 0.96 (0.72, 1.29), total serious adverse events, RR 1.00 (0.96, 1.05).**

The two outcomes assessing benefit (hip fracture and wrist fracture) were reported in 68% and 45% of women, respectively. In RCTs with mostly primary prevention women (mean age 68 years) bisphosphonates did not reduce hip fracture, RR 0.75 (0.48, 1.17) or wrist fracture, RR 0.96 (0.72, 1.27). In RCTs with mostly secondary prevention women (mean age 72 years) bisphosphonates reduced hip fracture, RR 0.60 (0.43, 0.83), ARR 1.0%, NNT 100 for 2.9 years and wrist fracture, RR 0.63 (0.45, 0.89), ARR 1.3%, NNT 77 for 3 years.

Outcomes assessing harm (withdrawals due to adverse effects and total withdrawals) were reported in 92% and 81% of randomized patients. These outcomes were not affected by bisphosphonates as compared to placebo: withdrawals due to adverse effects, RR 0.95 (0.89, 1.01), total withdrawals, RR 1.02 (0.98, 1.07).

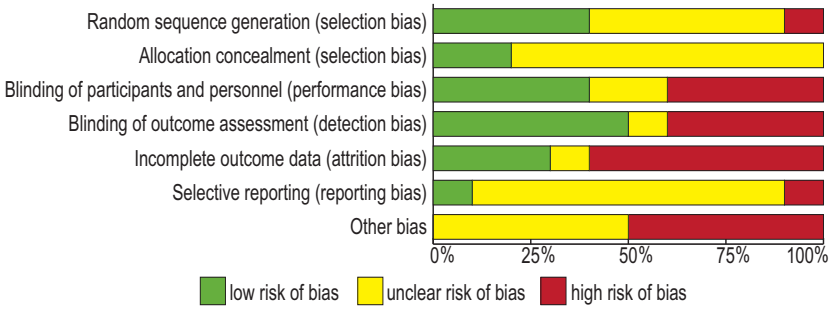
A subgroup analysis found no significant differences between the different bisphosphonates for each of the outcomes reported above. This is consistent with a class effect for the bisphosphonates and justifies the reporting of the pooled results.

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822•0700
Fax: 604 822•0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

Risk of bias was assessed for each of the RCTs using the Cochrane risk of bias tool. This revealed a high or unclear risk of bias in approximately 75% of the RCTs. This suggests that the small but statistically significant reduction in hip and wrist fractures seen in secondary prevention patients may not be real, or at best is an exaggeration of the real benefit (see Figure).

Figure: Risk of Bias for Hip fracture for secondary prevention



Discussion and Clinical Implications

A systematic review of all available RCTs showed no statistically significant reduction in hip or wrist fracture for women who have no prior fracture or vertebral compression at baseline. This represents the majority of women presently treated with bisphosphonates, most of whom are presumably being identified by bone mineral density measurements. The use of bisphosphonates in this population has been justified by effects on surrogate outcomes such as an increase in bone mineral density and a decrease in X-ray detected vertebral compressions, defined as a 15 or 20% reduction in the height of one or more vertebrae. As these surrogate outcomes have no impact on women's health, they were not included in our meta-analysis.

For secondary prevention, the incidence of hip and wrist fracture was decreased by bisphosphonates, however, the absolute magnitude of benefit is small, 1% for hip and 1.3% for wrist, and it is based on a potentially biased subset of randomized patients. Even if bisphosphonates actually result in these effects, how many women presented with a 1 in 100 chance over three years of preventing a hip fracture are likely to choose to take a bisphosphonate?

Hip fractures result in hospitalization and as such are serious adverse events. If bisphosphonates reduce hip fracture rates by 1%, this should be reflected in a 1% decrease in total serious adverse events. However, this review provides robust evidence that bisphosphonates do not cause a clinically significant reduction in total serious adverse events.

RR – relative risk
ARR – absolute risk reduction
NNT – number needed to treat

Three Cochrane reviews of these drugs [2-4] came to similar conclusions: no significant reduction in hip fracture for primary prevention and a small but statistically significant reduction in hip fracture for secondary prevention. However, the Cochrane authors defined primary and secondary prevention differently than our present review, made conclusions based on surrogate outcomes, and did not critically examine trial quality. Thus the reviews cannot be easily compared.

The present review of RCT evidence found no differences in mortality, total serious adverse events, withdrawals due to adverse effects or total withdrawals and would not be expected to detect infrequent serious harms. **Therapeutics Letter #84 will report on harms of biphosphonates obtained from spontaneous reporting and observational studies.**

Conclusions

• There are no proven clinically meaningful benefits for bisphosphonates in postmenopausal women without a prior fracture or vertebral compression.

• Because of the small magnitude of effect and the high risk of bias in the RCTs, it is unclear whether bisphosphonates cause a clinically meaningful reduction of hip fractures in women with a prior fracture or vertebral compression.

• For any new class of drugs indicated to prevent bone fractures, it is essential that a clinically meaningful reduction in hip fractures be demonstrated before licensing.

The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

1. Therapeutics Initiative. *Bisphosphonates: Do they prevent or cause bone fractures?* Therapeutics Letter. 2010 May- Aug 78: 1-2.
2. Wells GA, Cranney A, Peterson J et al. *Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women*. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD001155. DOI: 10.1002/14651858.CD001155.pub2.
3. Wells GA, Cranney A, Peterson J et al. *Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women*. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD003376. DOI: 10.1002/14651858.CD003376.pub3.
4. Wells GA, Cranney A, Peterson J et al. *Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women*. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD004523. DOI: 10.1002/14651858.CD004523.pub3.