



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

A Systematic Review of the Harms of Bisphosphonates

Therapeutics Letter #83 “A systematic review of the efficacy of bisphosphonates”¹ showed that the benefits of bisphosphonates are limited to postmenopausal women with a previous fracture or vertebral compression and are small in magnitude (see Table). The review also showed total serious adverse events were not decreased but specific serious harms of bisphosphonate therapy were not proven. Failure to prove harms in randomized controlled trials (RCTs) is not uncommon and as such the Cochrane Adverse Effects Methods Group recommends using other sources of data to properly document drug harms.² Concerns about serious adverse events (SAEs) from bisphosphonates were first raised in the early 2000s, about 5 years after alendronate was licensed in Canada.

Objective

To identify and quantify the serious harms associated with long-term use of alendronate (Fosamax[®]), etidronate (Didronel[®], Didrocal[®]) and risedronate (Actonel[®]).

Methods

Bibliographic databases were searched for systematic reviews of the following known serious bisphosphonate adverse effects: atypical fractures, osteonecrosis of the jaw, esophageal injury and esophageal cancer. Critical primary studies identified from the systematic reviews were appraised and summarized.

Findings

Atypical Femoral Fractures

The American Society of Bone and Mineral Research (ASBMR) Task Force defines atypical femoral fractures as requiring the presence of five major features: “location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete, and absence of comminution.”³ An FDA analysis included 7 non-randomized controlled trials and concluded that: “Atypical fractures, as defined by the ASBMR Task Force appear to have a strong association with bisphosphonates...”⁴ A systematic review of case reports and case series found that atypical femoral fractures were associated with prodromal thigh or hip pain, contralateral fractures, a mean age lower than that reported for typical (65 years) hip



fracture and commencement of therapy in younger women.⁵ Product monographs have been changed to reflect this serious adverse effect. A nested case-control study of older women in Ontario, Canada was used to estimate the yearly absolute risk increase (ARI) of atypical femoral fractures in patients receiving long-term bisphosphonate therapy.⁶ (see Table)

Osteonecrosis of the Jaw

Osteonecrosis of the jaw is defined as “the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks of identification by a health care provider.”⁷ The FDA reports that the incidence of this adverse effect in cancer patients treated with intravenous bisphosphonates for management of skeletal lesions is in the range of 1-5%. A FDA sponsored prevalence study found “a four-fold increased odds of osteonecrosis of the jaw in patients who used bisphosphonates for osteoporosis for 4 or more years compared to those who used the medication for less than 4 years OR=4.45, 95%CI (0.92 to 21.54).”⁷ This study was used to estimate the ARI in the Table.

Esophageal Injury

The manufacturer warned of alendronate-induced esophageal injury (defined as perforations, ulcerations, bleeding episodes or stricture) since market approval in 1995.⁸ At that time the manufacturer circulated an estimated incidence of 1.5% per year. It is possible that this serious adverse effect has been mitigated by warnings to take the drug on an empty stomach with sufficient water (120 ml) and to remain upright for at least 30 minutes after taking the drug. It is also possible that

Table: Estimated number of adverse events prevented or caused with long term bisphosphonate use

Event	ARR/year %	ARI/year %
Hip fracture ¹	0.3	
Wrist fracture ¹	0.4	
Atypical femoral fracture ⁶		0.1
Osteonecrosis of the jaw ⁷		0.1
Esophageal injury		0.1 – 1.5
Esophageal cancer ⁹		0.02

less frequent dosing regimens (weekly) have reduced this risk. We were unable to find estimates of the incidence of esophageal injury from current use of bisphosphonates. To reflect this uncertainty the Table shows a range for the estimate of ARI.

Esophageal Cancer

A 2010 nested case control study using a UK General Practice Research Database demonstrated a 1 per 1000 population increase in the risk of incident invasive cancer of the esophagus with 5 years of bisphosphonate use.⁹ We used this to estimate the ARI in the Table. To date the FDA remains undecided regarding the risk of esophageal cancer, though a safety warning has been issued and investigation is ongoing.

Clinical Implications

When investigating harms caused by drugs, the most difficult challenge is to estimate the magnitude of the harms so that they can be presented as absolute risk increases and compared to benefits presented as absolute risk reductions. The Table compares benefit estimates derived from the systematic review of RCTs, which compared 3 years of bisphosphonate treatment with placebo in women with a fracture (secondary prevention).¹ For contrast the Table also estimates the magnitude of the known serious harms from cohort and case-control studies. Because of the uncertainty in both estimates (high risk of bias in the benefit estimate¹) and the difficulty of estimating the magnitude of harm from non-randomized trials, it is

References

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impossible to give a precise estimate of net health effect. The best-case scenario is that the small absolute benefit is at least partially negated by the serious harm. **In fact the analysis is consistent with the finding that total serious adverse events were not reduced by bisphosphonates in the pooled RCTs, RR 1.00 (0.96, 1.05).¹**

The interpretation is complicated by the fact that the outcomes included are not of equal seriousness to patients. For example wrist fractures are not as serious as hip fractures, and atypical femoral fractures and serious esophageal events (stricture, perforation and cancer) are more serious than typical hip fractures. Another complicating issue is the duration of therapy. The benefits have only been demonstrated in RCTs averaging 3 years duration. **An RCT comparing alendronate with placebo following an initial 5 years of alendronate therapy showed no benefit from longer term alendronate treatment.¹⁰** The harms, osteonecrosis of the jaw and atypical fractures, are demonstrable after 4 years of bisphosphonate therapy. Therefore benefits likely predominate in the first 3 years, whereas harms likely predominate thereafter. This analysis does not include all known benefits of bisphosphonates, for example the potential long-term benefit of reductions in vertebral compression. Conversely it also does not include harms such as musculoskeletal pain, delayed or non-union of fractures, atrial fibrillation, etc. Many unanswered questions remain, but patients treated with bisphosphonates, or for whom this is proposed, should be informed of the magnitude and uncertainties of the benefits and harms.

Conclusions

- Systematic reviews assessing harms using observational studies are more difficult to conduct than traditional systematic reviews of RCTs assessing benefits.
- Bisphosphonates are associated with serious harms that are of similar clinical significance to their benefits.
- **In secondary prevention, the small benefits of bisphosphonates likely outweigh the harms during the first 3 years of therapy, but harms likely outweigh benefits for durations greater than 3 years.**

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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.