Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws

Woo S B, Hellstein J W, Kalmar J R

CRD summary
This review reported on cases of osteonecrosis of the jaws following treatment with bisphosphonates. The authors concluded that most reported cases have been in patients with multiple myeloma or metastatic cancer and, to a lesser extent, osteoporosis. The conclusions seem reasonable, though they are based on case series and prospective studies are required to reliably identify risk factors.

Authors' objectives
To review all case reports and case series of patients with bisphosphonate-associated osteonecrosis of the jaws.

Searching
PubMed was searched from inception to 31 January 2006 without any language restrictions; the search terms were provided.

Study selection
Study designs of evaluations included in the review
Case reports and case series were eligible for inclusion.

Specific interventions included in the review
Studies providing acceptable documentation of use of bisphosphonates were eligible (not further defined; studies were not required to provide details of the bisphosphonate used). In the majority of included cases, patients received intravenous bisphosphonates (mainly pamidronate and zoledronic acid).

Participants included in the review
Studies of patients with osteonecrosis of the jaws were eligible for inclusion. Studies were not required to provide information on the gender of the patients. In the majority of included cases, patients had multiple myeloma or metastatic breast cancer; others had osteoporosis or Paget disease.

Outcomes assessed in the review
Osteonecrosis of the jaw was the outcome of interest. To be eligible for inclusion, the studies were required to provide acceptable documentation of the disease, although information on the site of the lesion was not required.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review. Where authors had published more than one report of patients with osteonecrosis, they were contacted to identify whether the same patients had been included in multiple reports. Where this had occurred, only data from the larger, more recent publication was used.

Methods of synthesis
How were the studies combined?
The studies were discussed in a narrative synthesis.

**How were differences between studies investigated?**
Differences between the studies were reported in tables.

**Results of the review**
Twenty-nine papers (n=368) were included: 10 case series of 10 or more individuals and 19 series or case reports of fewer than 10 patients.

There were 368 reported cases of bisphosphonate-associated osteonecrosis of the jaw. The mandible alone was affected in 65% of cases, the maxilla alone in 26%, and both sites in 9%. In one third of cases the lesions were painless and there was a slightly higher proportion of females to males.

The most important risk factors were, according to the reviewers, type and total dose of bisphosphonate, history of trauma, dental surgery or dental infection. Ninety-four per cent of patients received pamidronate or zoledronic acid. Osteonecrosis occurred after having a tooth removed or other dentoalveolar surgery in 60% of cases; the remaining cases occurred spontaneously.

**Authors' conclusions**
Osteonecrosis of the jaws is a recently described adverse effect in patients treated with bisphosphonates and, in particular, potent aminobisphosphonates. Most of the reported cases have been in patients with multiple myeloma or metastatic cancer, though cases have also been identified in patients with osteoporosis.

**CRD commentary**
The review addressed a clear research question using defined inclusion criteria. Although there were no language restrictions, the sources searched for reported cases were limited and cases might have been missed. It was unclear whether appropriate steps to reduce error and bias were taken in the review processes, such as duplicated or checked study selection and data extraction procedures. However, appropriate efforts were made to minimise the risk of duplicate counting of single cases. A quality assessment was not conducted, but this aspect of systematic reviews of adverse events is still developing and there is no consensus yet as to how best to do this. The authors' conclusions seem reasonable despite being based on case series. Prospective studies are required to identify more precisely the risk factors for this adverse effect.

**Implications of the review for practice and research**
Practice: The authors recommended a number of management options for patients about to begin bisphosphonate therapy, those receiving treatment, and patients who already have osteonecrosis of the jaw. The systematic review did not investigate management options, therefore these are not summarised here.

Research: The authors stated that prospective studies are required to determine more precisely the risk factors for bisphosphonate-associated osteonecrosis of the jaws, clinical trials should clarify whether alternative dosing schedules reduce the incidence of osteonecrosis, and randomised controlled trials are needed to determine the most effective treatment options for patients who experience this adverse effect.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.