Commentary

Bisphosphonates – A Word of Caution

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Abstract

There have been recent reports from various centres of a possible association between avascular necrosis of the jaws and the use of bisphosphonates. This commentary reviews the available data and alerts clinicians to a possible adverse reaction in the oral cavity to a group of drugs that are commonly prescribed.

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Bisphosphonates are commonly prescribed for the treatment (and prevention) of postmenopausal and corticosteroid induced osteoporosis, Paget's disease, hypercalcemia associated with malignancy and osteolysis (and bone pain) associated with metastatic bone disease (e.g. in metastatic breast and prostate cancers).[1] The bisphosphonates available locally include pamidronate, risedronate, alendronate, zoledronate (containing nitrogen) and clodronate. The mode of action of these compounds is still unclear but they are known to inhibit osteoclastic function, induce apoptosis of osteoclasts, inhibit differentiation of bone marrow precursors into osteoclast and may have antiangiogenic effects, all of which, may contribute to inhibition of bone resorption and increase in bone mass.[1-3] It is only recently that the molecular targets and events associated with bisphosphonate use have been elucidated.[4,5]

Since late 2003, there have been reports in the literature of a possible association between bisphosphonate use and the appearance of avascular necrosis of the jaws.[6-10]

Wang et al,[6] in September 2003, first described cases of osteonecrosis of the alveolar bone in 3 female patients undergoing cancer chemotherapy for metastatic breast cancer. All 3 patients were also receiving pamidronate. Two of these patients developed bone necrosis after extractions, but the third patient apparently developed the condition spontaneously, resulting in an oroantral fistula. In all cases, histological examination of the lesions showed only necrotic bone with no evidence of metastatic disease. The authors, at that time, attributed the osteonecrosis to the cancer chemotherapy the patients were receiving. However, in a subsequent report,[7] the authors conceded, in view of similar reported cases after their publication, that the most likely cause of the osteonecrosis was the bisphosphonates.

About the same time as the initial report of Wang's group, Marx and co-workers,[8] reported a group of 36 American patients receiving intravenously either pamidronate or zoledronate for the management of bone disease associated with metastatic cancer, multiple myeloma and osteoporosis, who developed avascular necrosis of the jaws as well. In the majority of patients, this developed after extraction but in about 30% of cases, this event apparently occurred spontaneously.

Migliorati[9] reported a group of 5 patients, again on pamidronate or zoledronate, developing intraoral bone necrosis after dental extractions (2 patients) and in the remaining 3, without any identifiable local provoking factor.

Most recently, an oral and maxillofacial unit in Adelaide, Australia[10] reported 4 similar cases as well. The patients

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were either on pamidronate (3 patients) or alendronate (1 patient). Painful bone exposures, in all cases, developed after extractions involving the maxillary teeth.

In addition, there are increasingly more of such reports from various centres (personal communications, anecdotal reports and postings in the Bulletin Board of Oral Pathologists, etc).

From the above reports, the following points are made:

a) The patients usually have been receiving, in high doses, the more potent nitrogen-containing bisphosphonates, in particular, pamidronate and zoledronate.

b) These patients have advanced metastatic disease, some of whom may have also received chemotherapy and long-term glucocorticoids;[11] nevertheless, the reports cited above state that the use of bisphosphonates only is common to all the study patients.

c) There is limited data to suggest that the more commonly prescribed and less potent bisphosphonate, alendronate (Fosamax), may have similar, albeit less, effects on jaw bones as well.

d) This condition, to date, has been confined only to bones of the maxilla and mandible.

e) In cases of spontaneous bone necrosis, the most common site of involvement appears to be the posterior lingual aspect of the mandible over the mylohyoid ridge area.

f) Treatment of this painful condition is difficult and prolonged; the use of hyperbaric oxygen may not offer any additional benefit.

The possible role of bisphosphonates in the initiation of avascular bone necrosis, its newly discovered antiangiogenic properties, the impact of the duration, route of administration and dosages of such drugs and other risk factors contributing to the development of this condition are at this present time unclear.

In conclusion, avascular bone necrosis may *possibly* be an oral side-effect of bisphosphonate use. More data needs to be collected and proper case-control studies initiated before a causal relationship can be made. This is important in view of the current widespread medical use of bisphosphonates[12] and recent interests shown by dentists, as well, for the use of such drugs, particularly, in periodontal disease[13,14] and dental implantology.[13,15,16] The commentary above aims to alert the dental profession of a possible "drug-induced necrosis". Indeed, the dentist may well be responsible for initiating this condition and he/she must be able to recognise and treat it, using the best clinical evidence, when it becomes available. In the meantime, it would be prudent to take special precautions when carrying out surgical procedures in patients taking bisphosphonates, such as applying strict aseptic techniques, performing atraumatic surgery and achieving primary wound closure whenever possible.

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