Bisphosphonates and osteonecrosis of the jaw

Clinical records

The Adverse Drug Reactions Advisory Committee (ADRAC) has recently received 13 reports of osteonecrosis of the jaw associated with bisphosphonate use — 12 after intravenous bisphosphonate use, and one after oral alendronate use (Box). Ten of the reports implicated zoledronic acid, one pamidronate, and the other implicated both drugs in circumstances where the patient had switched from pamidronate to zoledronic acid.

In the nine cases with information on bisphosphonate dose, the monthly doses accorded with those recommended in the product information (90 mg of pamidronate, 4 mg of zoledronic acid). Time to onset varied from 1 month to more than 4 years, although most reports did not specify date of onset, possibly because onset was insidious.

Presenting symptoms included localised pain, numbness and altered sensation, exposed bone in the oral cavity, soft tissue infection and, in one case, loosening of several teeth. One report described a dental abscess after radiotherapy. All the reports described the osteonecrosis as occurring in the jaw; four specified the mandible, and two the maxilla.

With the exception of the report implicating oral alendronate for treatment of osteoporosis, the reports indicated that the bisphosphonate was being used in the context of malignancy.

Four reports documented dental extraction during bisphosphonate therapy in the months before the onset. One patient had had several teeth extracted because they had become loose during bisphosphonate therapy. A further report stated that onset of osteonecrosis occurred before dental extraction.

Many of the 13 reports were received soon after diagnosis, but, in at least four cases, the problem had persisted for 2 to 3 months after withdrawal of the bisphosphonate. None of the 13 patients had recovered at the time of reporting.

Recently, the United States Food and Drug Administration drew attention to the problem of osteonecrosis (also described as avascular or aseptic necrosis) of the mandible and/or maxilla, occurring in association with intravenously administered bisphosphonates used to control hypercalcaemia in metastatic bone disease.[1] In addition, two case series were published recently summarising 99 case reports of osteonecrosis of the jaw associated with bisphosphonates.[2,3] Combined with smaller case series, they bring the total reported to 129 cases.[4-8] Not all bisphosphonates have been implicated. Most commonly associated with the problem were zoledronic acid and pamidronate, possibly because these are the only intravenous bisphosphonates in widespread use, and because zoledronic acid has been approved for regular use in metastatic disease. However, seven reports implicated oral alendronate or risedronate used to treat osteoporosis.[4,6]

Osteonecrosis of the jaw closely resembles the occupational disorder "fossy jaw", which occurred in workers in match factories using white phosphorus in manufacturing.[9] The condition was distressingly painful, refractory to treatment and disfiguring to the extent that some sufferers committed suicide.

Bisphosphonates are not metabolised and have a strong binding affinity with osteoclasts. They can persist in bone for months and sometimes years after the drug has been discontinued. Accordingly, withdrawal of bisphosphonate therapy does not appear to hasten recovery of the osteonecrosis. Other treatments, including mouth rinses, systemic antibiotics, hyperbaric oxygen and surgical debridement have been tried, but so far none has proven consistently effective.

The mechanism underlying the reaction is unknown, but it has been postulated that bisphosphonates inhibit new vessel formation, thereby impairing healing. Although dental extractions and other oral surgery have been identified as precipitants in many cases, there is evidence suggesting that alveolar bone can be involved before, and independently of, such procedures. Indeed, the clinical presentation may closely simulate dental abscesses, "toothaches", denture sore spots, and osteomyelitis.

Documented risk factors include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy and corticosteroids) and comorbid conditions (eg, anaemia, coagulopathies, infection, and pre-existing oral disease).[10] Concomitant chemotherapy and corticosteroid treatment, in particular, may result in immunosuppression and thereby predispose to ongoing local sepsis after minor trauma.

Because this condition and its complications result in significant chronic pain, dysfunction and disfigurement which are difficult to treat, the focus should be on prevention. It is important that all health professionals, especially dentists, oncologists and oral surgeons, be aware of the possibility that patients being considered for dental extractions or other oral surgery are undergoing intravenous bisphosphonate therapy. Also, it is important for patients to be informed of the risk of this complication of bisphosphonate therapy, so that they have the opportunity to assess the need for dental treatment before starting therapy.[11] It is not known at this stage whether discontinuing bisphosphonates before major dental procedures can help prevent the problem, but, given the persist-

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Summary

- 13 cases of osteonecrosis of the jaw associated with bisphosphonate use have recently been reported to the Adverse Drug Reactions Advisory Committee.
- Most cases were associated with intravenous bisphosphonate therapy (11 cases with zoledronic acid and one with pamidronate), but one was associated with oral alendronate used to treat osteoporosis.
- The condition causes chronic pain, dysfunction and disfigurement; no treatment has proven consistently effective, and withdrawing the bisphosphonate does not seem to hasten recovery.
- The focus should be on prevention through attending to any necessary dental treatment before bisphosphonate therapy begins.

Clinical characteristics of 13 patients reported to ADRAC with osteonecrosis associated with bisphosphonate use

Age, sex	Bisphosponate used, other therapy	Indication for bisphosponate	Time to onset	Symptoms	Outcome
42, F	Zoledronic acid (4 mg IV every 3–4 weeks), capecitabine, celecoxib, ranitidine, radiotherapy	Breast carcinoma	6 months	Tooth abscess, osteoradionecrosis (site not specified)	Unknown*
46, F	Zoledronic acid (4 mg IV monthly), previously pamidronate (90 mg), dexamethasone	Breast carcinoma	4–6 months	Jaw necrosis (site not specified)	Not recovered†
46, F	Zoledronic acid (4 mg IV monthly)	Breast carcinoma	5 months	Maxillofacial pain, exposed bone in oral cavity, dental extractions, gingival swelling, impaired healing	Unknown†
57, M	Zoledronic acid (4 mg IV, frequency not stated), corticosteroids, chemotherapy	Prostate carcinoma	> 2 years	Exposed, painful bone in mandible, numbness, soft tissue infection	Not recovered‡
67, F	Alendronate (oral) prednisolone, leflunomide, celecoxib	Osteoporosis	ns	Maxillary alveolar necrosis, spontaneous loss of teeth, osteomyelitis, oro-antral fistula, condition recurred after surgery	Not recovered*
73, M	Pamidronate (90 mg IV monthly), thalidomide, corticosteroids	Multiple myeloma	1 year	Mandibular pain, hypoaesthesia, loosening of teeth, dental extractions, impaired healing, exposed bone	Slowly improving§
75, M	Zoledronic acid (4 mg IV, frequency not stated), corticosteroids, chemotherapy	Prostate carcinoma	> 2 years	Exposed, painful bone in mandible, numbness, dysaesthesia	Not recovered‡
79, M	Pamidronate (90 mg IV monthly), prednisolone, melphalan	Multiple myeloma	1 month	Mandibular pain, dysaesthesia, dental extraction, impaired healing, exposed bone, osteomyelitis, recurrent soft tissue infection	Not recovered†
80, M	Zoledronic acid (4 mg, reduced to 2 mg IV monthly)	Prostate carcinoma	8 months	Jaw necrosis (site not specified), recent dental surgery	Not recovered†
83, M	Zoledronic acid (4 mg IV monthly)	Prostate carcinoma	4.5 years	Jaw necrosis (site not specified)	Unknown†
ns, F	Zoledronic acid (dosage ns)	Breast carcinoma	ns	Jaw necrosis (site not specified) after two dental extractions	Unknown*
ns, F	Zoledronic acid (dosage ns)	Breast carcinoma	ns	Jaw necrosis (site not specified)	Unknown*
ns, M	Zoledronic acid (dosage ns)	Multiple myeloma	ns	Jaw necrosis (site not specified), exposed bone (spontaneous)	Unknown*

IV = intravenous. ns = not stated. * Not known whether patient continued bisphosphonate therapy after presentation. † Patient stopped bisphosphonate therapy after presentation. ‡ Patient continued bisphosphonate therapy after presentation. § Pamidronate was replaced by zoledronic acid, which was ongoing.

ence of bisphosphonates in bone, it is unlikely. Prescribers should also be aware that osteonecrosis of the jaw can occur in association with oral bisphosphonate therapy for osteoporosis.

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