Bisphosphonates, Osteonecrosis, Osteogenesis Imperfecta and Dental Extractions: A Case Series

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ABSTRACT

Over the past 4 years, numerous cases of osteonecrosis of the jaw in patients treated with bisphosphonates have been reported. Since 1998, children and adolescents with osteogenesis imperfecta have received bisphosphonates to increase their bone density and reduce the incidence of bone fractures. The results have been convincing, but recent reports of osteonecrosis of the jaw have caused great concern when these patients require dental extractions. The dental records of 15 children and adolescents with osteogenesis imperfecta, involving 60 dental extractions, mostly of primary teeth, done between 2001 and 2006, were reviewed. All patients but one had had or were having bisphosphonate treatment at the time of the extractions. No patient developed osteonecrosis. Further studies and data that allow clinicians to design adequate and safe treatment plans for this unique population are needed.

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The purpose of bisphosphonate therapy is to slow the rate of bone resorption. Mostly, this therapy is used to treat different types of cancers (myelomas, metastatic breast or prostate cancers), bone diseases or severe osteoporosis.[1,2] Since 2003, when the link between bisphosphonate therapy and bone osteonecrosis, and more specifically osteonecrosis of the jaw, was established,[3–5] many cases of osteonecrosis have been reported. Between September 2007 and May 2008, a search of PubMed yielded 141 articles and reviews on this subject. The authors of these articles caution clinicians to avoid oral surgery for patients undergoing bisphosphonate therapy and indicate that bone osteonecrosis, once established, is practically irreversible.[6–9]

Bisphosphonates are also administered to children and adolescents who have osteogenesis imperfecta. Osteogenesis imperfecta is often associated with severe dental problems, such as dentinogenesis imperfecta (gray-brown friable teeth, bulky crowns and early calcification of the pulpal space) and malocclusions (drastic open bites, impacted molars; **Figs. 1** and **2**). Bisphosphonate treatments contribute greatly to the well-being of these patients by reducing bone resorption and by controlling the pain associated with the condition. Bisphosphonate therapy has allowed many of these children to lead normal lives.[10,11] Osteogenesis imperfecta is not a common syndrome. The prevalence of all types combined is about 0.5 per 10,000 births. The group of 15 patients whom were reviewed correspond to a population of 300,000 people, probably more, since our group comprised children and adolescents exclusively.[12]

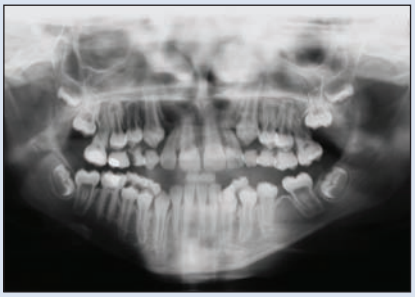

Figure 1: Panoramic view for patient no. 3 at age 12 years 9 months. Tooth 36 was abscessed and extracted 2.5 years earlier. Tooth 37 is drifting into the vacated space. The lower incisors show calcified canals indicative of dentinogenesis imperfecta.

Figure 2: Intraoral photograph for patient no. 3 at age 16 years, 4 months. Class III malocclusion and posterior open bites are frequent findings in patients with osteogenesis imperfecta. Dental discoloration is an additional feature with concurrent dentinogenesis imperfecta.

In the last few years, dental extractions in this group have been avoided because they may result in osteonecrosis of the jaw. Avoiding extraction, however, can cause chronic infection and pain. The question we examine in this paper is whether this avoidance is absolutely necessary.

Hundreds of patients with osteogenesis imperfecta are treated at the Montreal Shriners' Hospital. The dental department of the Montreal Children's Hospital follows and treats a large number of these children, who have unique dental problems that demand dental work, including dental extractions.

In this report, we review the oral health of children and adolescents with osteogenesis imperfecta who had bisphosphonate treatment after dental extractions and assess their risk of developing osteonecrosis of the jaw. The aim of this article was to briefly report the results of 60 such dental extractions to examine whether the numerous warnings against such treatment are warranted.

Method and Materials

The charts of all children and adolescents with osteogenesis imperfecta who had dental extractions at the Montreal Children's Hospital dental clinic between the years 2000 and 2006 were reviewed (except for 2 children who had their teeth extracted by private dentists). The results for a total of 15 patients (2 to 16 years of age), a total of 60 teeth, were examined. Many of the reported cases of dental extractions were done to eradicate dental infections and alleviate complications. No other treatment options were available. These children had regular follow-up at the Shriners' Hospital and to a lesser extent at the dental clinic of the Montreal Children's Hospital. Postoperative radiographs were not always taken. Because no complications were reported, we inferred that no osteonecrosis of the jaw occurred.

Most of the teeth extracted were primary. Some of these patients had bisphosphonate therapy at the time of the surgery. **Table 1** indicates the periods of therapy and the ages of the patients at the time of the extractions. Six patients underwent extractions at 2 different times. Their results are listed separately because the status of their bisphosphonate treatment was not similar at the time of the 2 surgeries. As a result, the 15 patients reviewed had their extractions done in 21 different sessions. The last column of **Table 1** indicates the period of treatment with bisphosphonate that the children received before the extraction, even though they were no longer undergoing treatment at the time of surgery.

Whether 1 child (patient no. 5) who had dental extractions was treated with bisphosphonate was unknown because he was treated in the United States and the information was unavailable. The status of another (patient no. 10) who was enrolled in a double-blinded study, was not known at the time of the surgery. We know now that he was on a placebo.

Results

None of the 15 patients reviewed developed osteonecrosis of the jaw. The healing time did not differ from what would be expected of normal healthy patients, and no complications were recorded. In 65% of the cases (12 sessions, 10 patients), the teeth were extracted while the children had active bisphosphonate treatment; in 23% of the cases (6 sessions, 4 patients), the extractions took place after the completion of the treatment; in 5% of the cases (1 session, 1 child), treatment status was unknown; in 7% of the cases (1 session, 1 adolescent), a placebo had been given. The radiographs of patient no. 3 show normal alveolar bone healing following the extraction of tooth 36 at age 10 years and 4 months and tooth 16 at age 16 years and 6 months (**Figs. 3** to **6**).

Discussion

Intravenous pamidronates are the bisphosphonates most often used for patients with osteogenesis imperfecta, in addition to orthopedic care and physiotherapy. They are prescribed only when the clinical findings are severe, for example, findings of repeated fractures (at least 3 within the previous year), vertebral compression fractures, deformities of the long bones, pain and ensuing lack of mobility.[13,14] The results of this treatment are immensely beneficial and have been widely published. Rauch and Glorieux[16] reported that the thickness of the cortical

Table 1 Patient characteristics, age at the time of extractions, teeth extracted, therapy and complications after surgery for the 15 patients reviewed

Pt no.	Sex	Age at extractions	Teeth extracted (tooth no.)	Bisph tx[a]	Antibiot cov	Complications after surgery	Age during bisph tx	Age at resumption of bisph tx
1	M	7 y 3 mo	72, 82	Yes	Yes	None	3 mo – 2 y 2 mo	5 y 8 mo
2	F	7 y 9 mo	55	No	U/K	None	1 y 10 mo – 6 y 9 mo	10 y 2 mo
2	F	8 y 3 mo	64, 65	No	U/K	None	1 y 10 mo – 6 y 9 mo	10 y 2 mo
3	M	10 y 3 mo	46[b]	Yes	Yes	None	6 y 2 mo – 12 y 9 mo	No bisph tx
3	M	15 y 4 mo	16[b]	No	Yes	None	6 y 2 mo – 12 y 9 mo	No bisph tx
4	F	9 y 6 mo	53, 63	Yes	Yes	None	3 mo – 5 y 3 mo	6 y 3 mo
5	M	18 y	18[b]	No	Yes	None	No bisph txt	No bisph tx
5	M	18 y 3 mo	28, 38[b]	No	Yes	Site infection (tooth 38); cleared	No bisph tx	No bisph tx
6	M	17 y 5 mo	18,[b] 48	No	Yes	None	15 y – 17 y	No bisph tx
6	M	18 y 1 mo	28,[b] 38	No	Yes	None	15 y – 17 y	No bisph tx
7	F	6 y 7 mo	51, 52, 62	Yes	No	None	1 y 11 mo – 7 y 11 mo	No bisph tx
8	M	9 y 5 mo	85	Yes	No	None	6 y 1 mo – 11 y	14 y 6 mo
8	M	9 y 6 mo	75	Yes	No	None	6 y 1 mo – 11 y	14 y 6 mo
9	M	13 y 9 mo	73, 74, 75, 83, 84, 85	No	Yes	None	3 y 5 mo – 12 y	14 y 2 mo
10	M	10 y 3 mo	51, 61, 71, 81	U/K	Yes	None	U/K	U/K
11	F	19 y 6 mo	37[b]	Yes	Yes	None	16 y 9 mo – 21 y 9 mo	No bisph tx
12	M	4 y 2 mo	51, 52, 54, 61, 62, 64	Yes	Yes	None	2 y 11 mo – 4 y 3 mo	No bisph tx
13	M	2 y	54, 64	Yes	Yes	None	0 y – 5 y	No bisph tx
13	M	2 y 5 mo	51, 52, 61, 62, 81, 82, 71, 72, 75	Yes	Yes	None	0 y – 5 y	No bisph tx
14	M	4 y 2 mo	71	Yes	Yes	None	5 mo – 4 y 6 mo	No bisph tx
15	M	6 y 7 mo	51, 52, 53, 54, 61, 62, 63, 64, 74, 84	Yes	Yes	None	5 y 4 mo – 9 y 4 mo	No bisph tx

Note: Pt no. = patient number; Bisph tx = bisphosphonate therapy; Antibiot cov = covered with antibiotic regimen at the time of dental surgery; U/K = unknown
[a]*Undergoing bisphosphonate therapy at the time of dental surgery.*
[b]*Surgical extractions.*

envelope of the iliac bone almost doubled during the first 2.4 years of administration of pamidronate. Parents coming to our clinic consistently comment on the sudden decrease in pain and fatigue that their children experience as soon as the therapy commences.[16]

Recent reports[8,9,17] of osteonecrosis of the jaw bones associated with bisphosphonate therapy have alarmed the dental community. Dental professionals hesitate to do extractions and orthodontics on these patients. A better understanding of the action of bisphosphonates (usually pamidronate) is required to determine when surgery should or should not be done. Bisphosphonates allow a better formation of bone because they decrease the activity of osteoclasts. Other actions of bisphosphonates include inhibiting the formation of the osteoclast precursors, encouraging the apoptosis of the osteoclasts and inhibiting their deposition on freshly exposed bone surfaces. All these functions, especially the latter, have an

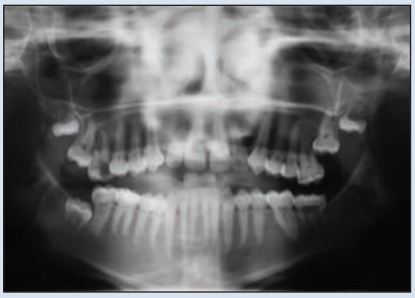

Figure 3: Panoramic view at age 16 years 4 months (patient no. 3). Tooth 16 is abscessed. Tooth 27 has not yet erupted. The maxillary incisors and the bicuspids show progressive pulpal calcification.

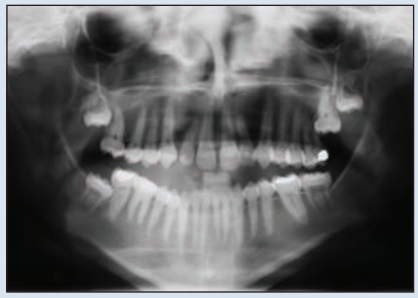

Figure 4: Panoramic view at age 17 years 3 months (patient no. 3), 11 months after the extraction of tooth 16. Tooth 17 has moved into the extraction space. Tooth 27 is still unerupted.

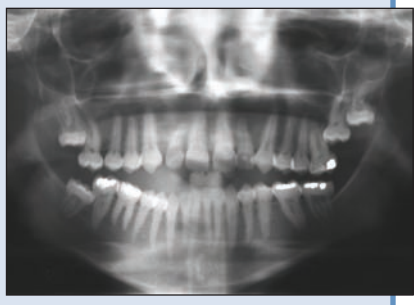

Figure 5: Panoramic view at age 18 years 6 months (patient no. 3). Teeth 18, 48, 27 and 28 are impacted.

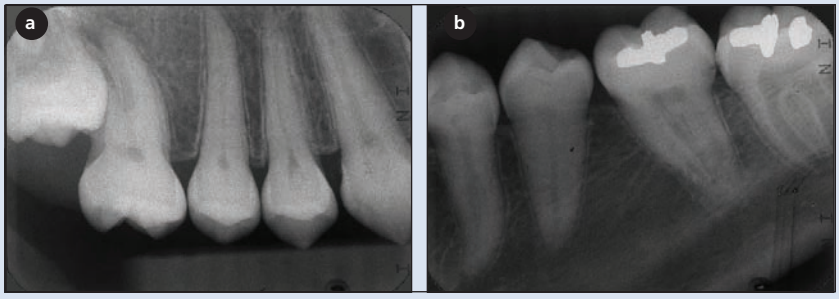

Figure 6: Periapical radiographs at age 18 years 6 months (patient no. 3): **(a)** upper right and **(b)** lower left quadrants. Tooth 36 was extracted 5 years 9 months earlier; tooth 16 was extracted 2 years 2 months earlier. Healing is apparently complete at both extraction sites. Generalized pulpal calcification is progressing.

impact on the remodelling of the bone, which is critical for proper bone healing.

When given in high dosages, bisphosphonates have another side effect: they show antiangiogenic activity and impede healing because the blood supply to the wound is diminished. Poor healing and osteonecrosis seem to be reasonable consequences of bisphosphonate treatment, particularly because the oral environment is so susceptible to postoperative infection. This susceptibility explains why bisphosphonate-induced osteonecrosis is invariably seen in the jaw after dental extractions when alveolar bone is exposed to the oral environment.

Khan and Khan[18] tried to establish a link between osteonecrosis of the jaw and bisphosphonate. They stated that 0.825% of the 4,000 cancer patients treated with intravenous bisphosphonates developed osteonecrosis of the jaw.[18] Other reviews report up to 11%.[19] In most surveys, it was evident that these patients were debilitated and that they had received high dosages of bisphosphonates, in addition to being given other drugs that could potentially aggravate the situation.[18,20] However, the exact dosage administered to the patients listed in these case reports is not clear. What is clear is that the occurrence of osteonecrosis of the jaw is linked to high dosages of bisphosphonates. This is understandable because the drug inhibits remodelling and slows the blood supply to a healing wound. Given enough drug, anyone could potentially develop the disease.

Intravenous pamidronate is the drug of choice for most patients with osteogenesis imperfecta. Dosages are precisely documented: 0.5 mg to 1.5 mg/kg, not exceeding 9 mg/kg annually. The drug is infused over a period of 3 days and repeated every 4 months. The system is estimated to be saturated after 3 to 4 years, at which point treatment is stopped. It may be resumed later if the child experiences new fractures, complains of severe pain or experiences overwhelming fatigue. The repeat treatment is always given at a lesser dosage. The main beneficial effect of pamidronate treatment occurs in the first 2 to 4 years of treatment.[21]

Other bisphosphonates have been used, such as zoledronate, alendronate and risedronate.

Patients with osteogenesis imperfecta did not receive nearly as high a dosage of bisphosphonates as those patients who developed osteonecrosis of the jaw.

In this review, healing was unremarkable in all cases, except for the patient with osteogenesis imperfecta who had the third molar removed and had not been exposed to bisphosphonates. Neither were there any reports of complications after dental extractions done on over 300 patients with osteogenesis imperfecta at the Shriners' Hospital.[22]

Further, the children in our review who were not on bisphosphonates at the time of surgery had previously been treated with bisphosphonate (except for the one on placebo and the one of unknown status for treatment with bisphosphonate). The interval between the end of their medical treatment and their dental surgery ranged from 5.5 months to 2.5 years. This finding is interesting because bisphosphonates are retained in bone for long periods of time, even years.[1,6,8] In theory, exposure to bisphosphonate treatment before dental extractions would increase the risk for bone osteonecrosis. In our experience, bone osteonecrosis did not occur and our results did not demonstrate this trend.

Our findings do not mean that precautions should not be taken during oral surgery. Because patients with osteogenesis imperfecta are at greater risk for fractures, the surgery should be as atraumatic as possible. The surgery should not be scheduled immediately before treatment with bisphosphonates because of the high affinity of the drug during bone healing. At the Shriners' Hospital, the following orthopedic protocol has been developed: when osteotomy procedures are planned, administration of bisphosphonates is delayed for 4 months after surgery (osteotomies are done when long leg bones must be straightened before rods are placed). For an extraction, waiting 8 to 15 days after the last infusion of the medicine is recommended. In our department, prophylactic antibiotics are also administered before dental surgery because the oral flora is aggressive and may hinder healing. In addition, a good radiograph of the surgical site should be taken to confirm healing before more bisphosphonates are administered.

The young patients with osteogenesis imperfecta reviewed for this study were otherwise healthy. They received smaller bisphosphonate dosages for a shorter time than those reported in the literature. These factors may place this group of patients at a lower risk of developing bone osteonecrosis.

Osteonecrosis of the jaw is not a pediatric disease, as far as we know. Lam and others[23] concur: "In pediatric patients, intravenous bisphosphonates are used in the management of osteogenesis imperfecta, idiopathic juvenile osteoporosis and osteopenic patients with juvenile rheumatoid arthritis who receive large doses of corticosteroids or methotrexate. However, unlike in adults, at the present time bone osteonecrosis is thought to occur rarely, if at all, in children."

Conclusion

Osteonecrosis of the jaw is a serious condition; its treatment with bisphosphonate therapy cannot, therefore, be taken lightly. On the other hand, a person receiving bisphosphonate treatment who needs dental surgery, dental work or orthodontic intervention cannot be deprived of such dental work solely on the grounds of potential complications. In elective treatment, the more invasive the treatment, the greater the grounds for concern. For example, we know nothing about the risk of osteonecrosis of the jaw with dental implant treatment or with long-term administration of pamidronate. We cannot conclude from this report that dental extractions done on patients with osteogenesis imperfecta are risk-free, but we can conclude that further studies are necessary to analyze the dosage and other factors required to recommend appropriate treatment.

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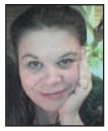

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