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The Risk of Bisphosphonate-Related Osteonecrosis of the Jaw in Children. A Case Report and Literature Review

Abstract: Bisphosphonate use has been described in children diagnosed with osteogenesis imperfecta (OI), fibrous dysplasia, neuromuscular disorders, bone dysplasia, idiopathic juvenile osteoporosis, rheumatologic disorder and even Crohn's disease. In OI patients, bisphosphonates have become an important symptomatic therapy for moderate and severe forms of the disease, because their inhibitory effect on osteoclasts increases bone mineralization and density, thereby reducing the risk of bone fractures. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) has become an increasingly common complication as the use of these drugs is becoming more widespread in adults. However, the evidence for BRONJ in paediatric patients is scarce. We present a case of a patient with OI on IV bisphosphonate therapy who required dental extractions and review the literature of the risk of BRONJ in this group of patients.
Clinical Relevance: Dental clinicians need to be aware of the potential risk of BRONJ in paediatric patients who have had intravenous bisphosphonate therapy. It is important that these patients are identified and managed appropriately.
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Osteogenesis imperfecta (OI) is part of a group of disorders characterized by increased fragility of bone. OI sufferers are born with defective connective tissue or without the ability to make connective tissue. In some cases, the collagen may be of poor quality, or there may not be enough to support the mineral structure of the bones. Historically, OI has been viewed as an autosomal dominant disorder of type-I collagen. The majority of cases are caused by a dominant mutation to type 1 collagen (COL1A1 or COL1A2) genes. In recent years, there has been the identification of autosomal recessive forms. Two of the recessive types of OI, types VII and VIII, do not involve mutations in the type-I collagen genes. These recessive types of OI result from mutations in two genes that affect collagen: the cartilage-associated protein gene (CRTAP) and the prolyl 3-hydroxylase 1 gene (LEPRE1). There are currently eight different types of OI. The severity of OI ranges from lethal form to milder form and the symptoms vary from person to person. OI type I is the mildest and the most common form of the disorder. OI type II is the most severe form. The estimated prevalence of OI is around 1 in 20,000 to 1 in 30,000 births.[1] There are a few dental abnormalities associated with OI. These patients tend to have skeletal Class III malocclusion and often have an open-bite. Tooth development can also be affected, with tooth eruption being delayed or advanced. Permanent molars may fail to erupt or erupt ectopically. In some cases, OI is also associated with dentinogenesis imperfecta (DI). Teeth that are affected by DI are usually discoloured, ranging from amber-brown to grey-blue. The enamel

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may be hypomineralized and tends to crack away from abnormal dentine. As a result teeth that are affected by DI are prone to attrition.[2]

The management of OI is usually undertaken as a multidisciplinary effort consisting of occupational therapy, orthopaedic surgery, appropriate physiotherapy and family support. Some success has been achieved through medical treatments that strengthen bone and thus reduce the number of fractures and bone deformities.

Bisphoshonates are used commonly for a range of conditions including osteoporosis, Paget's disease of bone, hypercalcaemia, metastatic cancer affecting the bone and OI. For OI patients, bisphosphonate therapy was first used in the early 1990s.[3] A number of studies on the use of bisphosphonates in OI patients have shown that they have an important role in the symptomatic control for severe forms of the disease.[4,5] Bisphosphonate therapy increases bone density by irreversibly binding to bone and inhibiting the function of osteoclasts. This results in a net increase in bone mass and mineralization. In the majority of cases, an increase in bone density is seen with vertebral body remodelling, an early reduction in bone pain and improved mobility. Pamidronate is a commonly used bisphosphonate in children. It is used to prevent bone loss and to strengthen bone. It is used in several other conditions in which generalized osteoporosis occurs: idiopathic juvenile osteoporosis, osteoporosis pseudoglioma syndrome, polyostotic fibrous dysplasia and steroid-induced osteoporosis.

The number of patients who receive bisphosphonate therapy is increasing. Many general dental practitioners are hesitant to carry out dental extractions and other oral surgical procedures on patients receiving bisphosphonates owing to the possibility of BRONJ. Currently, there are no guidelines or general consensus in the optimum management for this group of paediatric patients. The perceived wisdom is that dental extractions and other oral surgical procedures in this group of patients should be carried out only when it is absolutely necessary, and is based on the management of adult patients receiving bisphosphonate therapy. However, avoiding or delaying dental extractions of unrestorable teeth can result in chronic pain and infection which of itself can have serious consequences, and failure to intercept or manage evolving malocclusions by not performing dental extractions may effectively deprive paediatric patients of a functional occlusion.

Case report

A 12-year-old Caucasian girl was referred to the oral and maxillofacial unit at Kent and Canterbury Hospital in April 2010 as her dentist was concerned about the delayed eruption of her permanent teeth, ectopic position of her permanent canines and the hypodontia associated with OI. The patient's main concern was the generalized spacing of her dentition.

The patient had been identified as potentially having OI when bilateral femoral fractures were identified on her *in-utero* 20 weeks anomaly scan, and follow-up scans suggested further femoral fractures, which subsequently healed. She was delivered by elective caesarean section at 37 weeks gestation to avoid further bony injuries. There was an extensive paternal family history of relatives affected with OI. Her father had sustained several long bone fractures during his infant and teenage years, her paternal grandfather had a history of multiple fractures and had a hearing impairment since his twenties. Other relatives, including a great paternal grandmother, several cousins, uncles and aunts were also affected. Some of the affected individuals had deafness only, others 'brittle bones' only, whilst other members had both.

At six years old, thoracic and lumbar spine radiographs revealed wedging and partial collapse of T4 and T6 vertebral bodies and loss of vertebral body height at T7, T8, T9, L1 and L3. A year later, she was reviewed in the OI clinic at the Great Ormond Street Hospital for Children; skeletal radiographs showed generalized osteoporosis with generalized thinning of the cortex with slender long bones and ribs. Multiple vertebral bony compression fractures were present affecting most of the vertebrae in the thoracic region and also L1, L2 and L4. As she continued to have episodes of back pain, the consultant paediatric neurologist felt she would benefit from intravenous bisphosphonate therapy and she received a three monthly pamidronate dose regime of 1 mg per kg per dose for three days every three months.

At presentation, the patient reported many symptoms associated with OI, including excessive sweating, particularly at night, extreme ligamentous laxity affecting her hands, fingers, hips, knees and ankles. Many of her fine motor difficulties have been attributed to her extremely flexible joints. Since birth she had a tendency to bruise easily. Her medication regime included regular pamidronate infusions, Cacit-D3 calcium and vitamin D supplements, pizotifen and rizatripta for recurrent migraines, and regular paracetamol and ibuprofen for back pain.

General clinical examination revealed the classic blue sclerae of OI. Her dental examination revealed a Class I occlusion on a skeletal I base with reduced lower facial height and bimaxillary proclination. She was in the mixed dentition stage of development with notable spacing. She had a Class I incisal relationship with a 4 mm overjet, with increased and complete overbite. Teeth present clinically were:

6 E D C 2 1 | 1 2 C D E 6
6 E D 3 2 1 | 1 2 C D E 6

Teeth present radiographically but unerupted were:

7 5 4 3 | 3 4 5 7
5 4 | 3 4 5

Radiographically, all permanent third molars (UR8, UL8, LR8 and LL8) and lower permanent second molars (LR7 and LL7) were missing. Both upper permanent canines (UR3 and UL3) were ectopically placed and appeared to have follicular enlargement.

Orthodontically, it was felt that the patient was too young for comprehensive treatment, and that orthodontic treatment should be restricted to just closing the space labially. Despite the history of IV bisphosphonate use, it was agreed that the upper deciduous canines (URC and ULC) and all deciduous first molar teeth (URD, ULD, LRD and LLD) should be extracted in order to facilitate the eruption of the permanent successors (Figure 1). This was completed atraumatically under general anaesthetic. Post-op the patient was prescribed a 5-day course of amoxicillin to prevent post-operative infection.

The extraction sites were reviewed a month and then 3 months after the procedure. All the extraction sites had

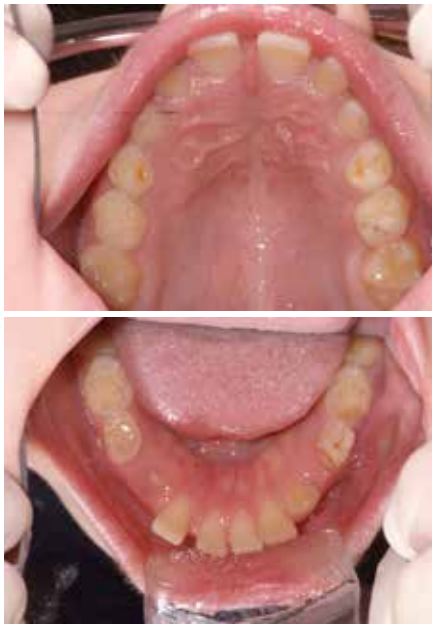

Figure 1. (a, b) Pre-operative clinical photographs showing retained upper deciduous canines (URC and ULC), upper and lower deciduous first molars (URD, ULD, LRD and LLD). (Courtesy of Mr James Farley, Clinical Photographer, East Kent Hospitals University NHS Foundation Trust.)

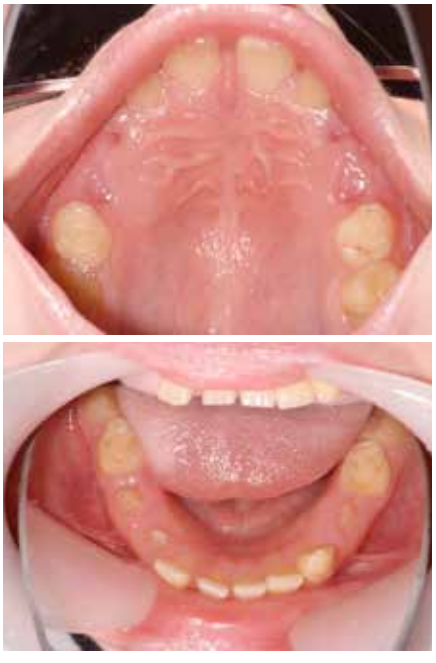

Figure 2. (a, b) Post-operative (3 months after the procedure) clinical photographs showing extraction sites of retained upper deciduous canines (URC and ULC), upper and lower deciduous first molars (URD, ULD, LRD and LLD) healed uneventfully. (Courtesy of Mr James Farley, Clinical Photographer, East Kent Hospitals University NHS Foundation Trust.)

healed very well with no signs of infection, exposed bone or osteonecrosis (Figure 2).

Literature review and discussion

The management of paediatric patients on bisphosphonate therapy is extrapolated from adult patients as there is little reported in the literature on paediatric cases. Adult patients take bisphosphonates for a variety of reasons, but the main conditions are osteoporosis and bony metastatic cancer. It is recognized that those on IV bisphosphonates, and those taking oral bisphosphonates for more than 3 years are at risk, and particularly those concomitantly taking steroids.

Previous articles in *Dental Update* have discussed and highlighted the risk of BRONJ in adult patients who have a history of bisphosphonate treatment.[6-10] The risk of developing osteonecrosis of the jaw is low in adult patients on oral bisphosphonates (reported as between 1:10,000 to 1:100,000 patients). In contrast, the incidence is between 1:10 to 1:100 in adult patients on intravenous bisphosphonates for metastatic cancer to the bone.[11] Currently, there are just four relevant retrospective analyses on the risk of osteonecrosis of the jaw in children and adolescents who have received intravenous bisphosphonate treatment for non-malignant conditions.

Chahine *et al*[12] presented a study of the healing of dental extraction sockets in 66 paediatric patients who had been treated with intravenous pamidronate at the Shriners Hospital for Children in Montreal between 1992 and 2006. All patients received at least one cycle of intravenous pamidronate for various medical conditions: 79% of them were diagnosed with OI; other diagnoses included fibrous dysplasia, neuromuscular disorders, bone dysplasia, idiopathic juvenile osteoporosis, rheumatologic disorder and Crohn's disease. The duration of their intravenous bisphosphonate therapy ranged from less than a month to 11.2 years. The cumulative dose of intravenous pamidronate ranged from 2.5–81 mg/kg body weight. A total of 250 dental extractions was carried out on these patients. The sites of surgery were not stated: 15% of these procedures involved flap elevation, bone removal and tooth sectioning. Pre-operative prophylactic antibiotics were given in 16% of cases and no patients were given post-operative antibiotics. Follow-up data was presented for 225 of these dental extractions, with a range of 3–1370 days post-surgery, where there were no reports of delayed healing, exposed bone or osteonecrosis of the jaw.

A different group of 15 patients with OI who had dental extractions at the Montreal Children's Hospital Dental Clinic between 2000 and 2006 has been reviewed by Schwartz *et al*.[13] The age range of these patients at the time of dental treatment was between 2 and 16 years of age. A total of 60 extractions was carried out in this study: 65% while the patient was having active intravenous bisphoshonate treatment. In 23% of cases, extractions took place after the completion of bisphosphonate treatment. All the patients were reviewed regularly after their extractions. Post-operative radiographs were not always taken. None of the cases developed any infection, delayed healing or osteonecrosis of the jaw.

Brown *et al*[14] assessed a group of 42 paediatric patients with a history of intravenous bisphosphonate therapy who underwent various dental procedures. This group of patients was treated at the Department of Endocrinology at the Royal Children's Hospital in Australia: 82% of them were diagnosed with OI.

Other diagnoses included osteoporosis pseudolioma syndrome, McCune Albright syndrome and transverse myelitis. All patients received intravenous bisphosphonates between 2002 and 2006. They all received active disodium pamidronate (APD) or zoledronic acid (ZA) infusion. Thirty-seven patients received APD at 1 mg/kg/dose at a mean cumulative dose of 19.8 mg/kg, and ZA at 0.05 mg/kg/dose at a mean cumulative dose of 0.49 mg/kg. Four patients received ZA alone and one received APD alone. Full dental examinations were carried out on every patient post-operatively and there were no reported cases of osteonecrosis of the jaw. Dental procedures that were carried out included simple extraction of deciduous and permanent teeth, surgical extraction of permanent teeth and surgical exposure of upper canines. Radiographs were taken when clinically indicated.

Another paper from the Pediatric Dentistry Graduate Clinic at the University of North Carolina School of Dentistry reports a case of a 6-year-old male with a history of OI and DI who underwent the extraction of two upper deciduous molars and one lower deciduous molar under general anaesthetic.[15] The patient was receiving intravenous pamidronate at the time of surgery and was given prophylactic ampicillin pre-operatively. He was reviewed a month after the general anaesthetic and all the extraction sites were healing without any clinical signs of BRONJ.

Thus, on the basis of a small sample of 124 patients who received oral surgical procedures, it would appear that the risk of BRONJ in children and adolescents receiving oral surgical procedures, having been treated with intravenous bisphosphonates, is extremely low in comparison with adult patients. Though we must bear in mind that this may be because this group of patients does not have some of the other risk factors seen in adult patients, such as malignant disease, concomitant steroid use and frailty. This may indicate that paediatric patients have a different risk profile from a medical perspective, but they may also have a different dental risk profile.

Many of the procedures reported will have involved deciduous teeth. As noted in the case presented, the delayed eruption of permanent teeth has been recognized in patients receiving bisphosphonate therapy.[16-17] This may result in an increased incidence of retained deciduous teeth. Deciduous teeth have shorter and narrower roots than permanent teeth and many of these teeth may have also had some degree of root resorption. Thus, the bony extraction socket is smaller and there is less exposed bone to be resorbed. The paediatric alveolar processes are also growing, with active bone deposition, which may also help these sockets to heal, even if there are areas of bone in the sockets which cannot be resorbed as a result of the bound bisphosphonate.

The majority of extractions for adult patients will be for grossly decayed or abscessed teeth and those with periodontal disease. In children, particularly those under the care of specialist children's medical units, there will be ongoing dental care and supervision and there is a smaller likelihood that the extractions will be for dental abscess. As discussed previously, the extractions are more likely to be for retained deciduous teeth, orthodontic treatment or in those with concomitant DI (dental extractions may be needed due to loss of enamel and poorly mineralized dentine). Thus the extraction or surgical sites are less likely to have infection present within the bony socket at the time of extraction, which might further modify healing.

The use of perioperative and post-operative antibiotics also seems to be debatable in this group. Although several authors do not specifically mention antibiotic usage,[13,14] the vast majority of patients reported by Chahine *et al*[12] did not receive antibiotics and no cases of BRONJ were found.

As this group of patients grow older, the duration of bisphosphonate use and thus cumulative dose will increase. This has the potential to increase the risk of this patient group developing osteonecrosis of the jaw as adult patients. It remains to be seen whether the apparent low incidence of BRONJ in these patients as children and adolescents will be seen as adults. More studies are needed to establish whether there is a host resistance to osteonecrosis or better biological healing in this patient group. Additional studies and long-term randomized controlled clinical trials will help to formulate guidelines and promote a safe approach in managing the oral health of this group of patients.

Whilst this article primarily considers the use of intravenous bisphosphonates in children, it should be noted that the newer monoclonal antibody agents, such as Denosumab, currently licensed for use in metastatic bone cancer, may yet be used in other conditions, such as OI.[18] There are already reported cases of osteonecrosis of the jaw associated with these agents in adults.[19,20] We must therefore be aware of the potential risk of osteonecrosis of the jaw associated with these agents in children if they become commonly used on children with OI in the future.

The current thinking on orthodontic treatment for patients who have a history of oral or intravenous bisphosphonates therapy was reviewed by Abela *et al*.[21] This article indicates that bisphosphonates have a strong inhibitory effect on tooth movement. This theory is mainly based on animal experimentation, where studies on rats and mice have shown that the effect of bisphosphonates on osteoclastic activity results in decreased resorptive areas after orthodontic force application. It is believed that this is dose-dependent. Therefore, it is suggested that it is wise to establish the response to orthodontic forces at the beginning of orthodontic treatment for this group of patients. This article recommends that a careful risks/benefit analysis should be undertaken jointly between the orthodontist and medical physician prior to any orthodontic treatment in this group of patients. Although orthodontic treatment is not thought to cause BRONJ, Abela *et al*[21] recommend orthodontic treatment should be performed on a non-extraction basis and focus on the alignment of the labial segments to minimize the risk of BRONJ.

Conclusion

There seems to be a reduced risk of the development of bisphosphonate-related osteonecrosis of the jaws in children and adolescents. The reasons for this are not clear. However, a review of the literature would suggest that this patient group should not be deprived of oral surgery procedures solely on the grounds of the possible risk of osteonecrosis. Prior to any oral surgery procedures, general dental practitioners should explain to the patient and his/her parents about the potential risk of BRONJ as part of informed consent. It should be documented clearly in the patient's record. Follow-up appointments must be arranged so that the healing of the surgical site is monitored closely. If the patient develops BRONJ, referral to secondary care for assessment and management is required.

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Book Review

Oral and Maxillofacial Medicine, the Basis of Diagnosis and Treatment 3rd edn. By Crispian Scully. Oxford: Churchill Livingstone Elsevier, 2013 (448pp; £49.99p/b). ISBN 978-0-7020-4948-4.

This book, from our most prodigious dental author, is now in its 3rd edition. Crispian Scully has set out ambitious aims to produce a text that will: i) aid the clinician in the diagnosis of the common as well as the more serious oral disorders; ii) suggest appropriate investigations to help confirm the diagnosis; and iii) provide management regimes and/or suggested referral pathways, to complete the patient care package.

To achieve these lofty aims there is much cross-referencing between chapters utilizing tables and algorithms: taking, for example, *the single ulcer*, the clinician can turn to section 2 (*Common complaints*), follow the appropriate algorithm and be led towards the more serious diagnosis in section 3 (*Potentially malignant disorders*), or towards a non-neoplastic diagnosis with management regimes, found in section 4 (*Common and important orofacial conditions*). Examples of suitable 'patient information sheets', as well as useful websites, are provided at the end of each chapter for the benefit of both patient and clinician.

In an added attempt to keep the book contemporary and relevant, reference is made to emergent therapies and also complementary medicine products. At the end of each chapter, a reference section provides a further resource for those wishing to examine the evidence base underpinning this extensive work.

It is not surprising that previous editions of this book, that now runs to over 400 pages, have won awards and plaudits since it was first published in 2004.

To whom would I recommend this book? I would not necessarily recommend that this book needs to be read cover to cover unless it is of specialist interest, however, practising clinicians may need to justify why they do not own such a valuable reference book rather than why they do. In the interest of your patients and your own erudition you would do well to have this tome close to hand in your office.

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