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Effects of bisphosphonates on tooth eruption in children with osteogenesis imperfecta

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Bisphosphonates are currently used in the therapy of osteogenesis imperfecta (OI) to decrease the bone fragility observed in OI patients. Bisphosphonate therapy delays tooth eruption in rats. The aim of this study was to determine whether or not bisphosphonate therapy delays tooth eruption in children. The clinical emergence of teeth was observed and the calculated dental age and the number of delayed teeth were determined for 33 OI patients treated with bisphosphonates and for strictly gender- and age-matched controls. There were significant differences between bisphosphonate-treated patients and controls for calculated dental age and number of delayed teeth. Bisphosphonate therapy was associated with a mean delay of 1.67 yr in tooth eruption in children with OI.

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Osteogenesis imperfecta (OI) is an inherited disorder of the connective tissue caused by mutations in either the collagen Iα1 gene on chromosome 17 or the collagen Iα2 gene on chromosome 7 (1). The reported incidence of OI is between 6 and 20 per 100,000 newborns (2). The disease is usually inherited in an autosomal-dominant manner, although *de novo* mutations are common. Patients with OI may show any of a range of signs related to defective collagen, including bone fragility, growth deficiency, blue sclerae, hearing loss, joint laxity, and dentinogenesis imperfecta type I and other dental abnormalities such as agenesis (3), apically extended pulp chambers (4), impaction (5, 6), invagination (4), and denticles (4, 7, 8). Tooth eruption was found to be age-appropriate in all but one of the 68 index patients recently studied (9) and in all 27 OI patients described in a previous study (6).

Bisphosphonates are currently used to decrease bone fragility in OI patients. Bisphosphonates have the unique property of inhibiting the ability of osteoclasts to resorb bone *in vitro* (10) and to resorb long bones *in vivo* (11). Studies of osteopetrotic rodents suggest that localized alveolar bone resorption is a requirement before tooth eruption (12). Bisphosphonates inhibit bone resorption and thereby delay tooth eruption of both molars and incisors in rats (13).

In this study we sought to determine whether OI patients experience delayed tooth eruption as a result of bisphosphonate therapy.

Material and methods

The study population consisted of children with OI who were registered in French and Belgian patient groups (Association de l'Osteogenese Imparfaite, Association Francophone Belge de l'Osteogenese Imparfaite). An OI child was included if any one of the permanent teeth had fully emerged. The group of OI patients consisted of 33 children (12 boys and 21 girls), 6.2–14.6 yr of age, who received nitrogen-containing bisphosphonate therapy because they had experienced numerous fractures. The cumulative doses administered to OI patients ranged from 3 to 90 mg kg^{-1}, with a mean of 29 mg kg^{-1} and a median of 27 mg kg^{-1}. Sex-matched and age-matched controls were recruited from the French general population. The age difference between an OI patient and his control was < 0.05 yr in 16 cases and < 0.10 yr in 17 cases. The OI patients were classified as OI types I, III, and IV as defined by Sillence *et al.* (14). This study protocol was approved by a local Ethics Committee, and informed consent was obtained from the mother or the father of the children.

Each child underwent a visual inspection under natural light for the presence of permanent teeth. Dentinogenesis imperfecta was present in 15 of our OI patients. The status of each tooth was recorded on a diagram of the permanent dentition using a scale of 0–1, as follows, adapted from Carvalho *et al.* (15): 0, tooth not present; 0.5, tooth partially erupted and less than half of the facial surfaces covered by gingival tissue; 1, tooth fully emerged and in occlusion. The number of delayed teeth was determined using the classical data of Hurme (16). A tooth was described as delayed if it had not emerged in the range of age given by Hurme (16).

The method used to assess dental age was based on the number of permanent teeth that had emerged; data were collected for girls and boys between 5.8 and 12.9 yr of age (17). The dental age of individual subjects was determined on the basis of the mean age corresponding to the number of emerged permanent teeth, using the data of Hägg & Taranger (17).

The paired *t*-test was used to test the hypothesis that the chronological age and the dental age of matched pairs were identical, and also to test in the controls the relationship between chronological age and dental age. The chi-square test was used for comparison of the number of delayed teeth between OI patients and controls, for comparison between low and high doses of bisphosphonate therapy, and for comparison between patients with or without dentinogenesis imperfecta.

Results

The accuracy of assessment of chronological age by analysis of tooth emergence was checked in the control group. There was no significant difference between the calculated dental age and the chronological age (paired *t*-test: $t = 0.60$). No significant difference was observed for the chronological age between OI patients and their matched controls ($t = 0.44$, paired *t*-test). Patients and controls showed significant differences concerning the calculated dental age {1.47 ± 0.22 [standard error of the mean (SEM)] yr; paired *t*-test: $t = 7.00$, $P \ll 0.001$}; the number of permanent teeth erupted {[4.21 ± 0.58 (SEM) teeth; paired *t*-test: $t = 7.32$, $P \ll 0.001$]; and the number of delayed teeth [1.58 ± 0.42 (SEM) teeth; paired *t*-test: $t = 3.87$, $P \ll 0.001$])}.

Figure 1 shows chronological age and calculated dental age (17) for all the children. The mean (± SEM) tooth eruption delay was 0.009 ± 0.07 yr for controls and 1.67 ± 0.40 yr for bisphosphonate-treated OI patients ($P \ll 0.001$). Table 1 shows the number of delayed teeth in OI patients and the controls. Statistically significant differences were observed between controls and OI patients as assessed by the chi-square test ($P < 0.01$). No difference was observed between OI patients with or without dentinogenesis imperfecta. When the OI patients were separated into two groups according to the median of the cumulative bisphosphonate dose received (27 mg kg^{-1}), a significant difference between the low-dose and high-dose groups was observed, such that the high-dose group had significantly more delayed teeth. No statistical differences were found in the ages of OI patients: in the low-dose group, 8.7 ± 0.54 (SEM) yr for patients without delayed teeth and 9.06 ± 1.04 (SEM) yr for patients with delayed teeth; and in the high-dose group, 10.26 ± 1.59 (SEM) yr for patients without delayed teeth and 9.93 ± 0.18 (SEM) yr for patients with delayed teeth.

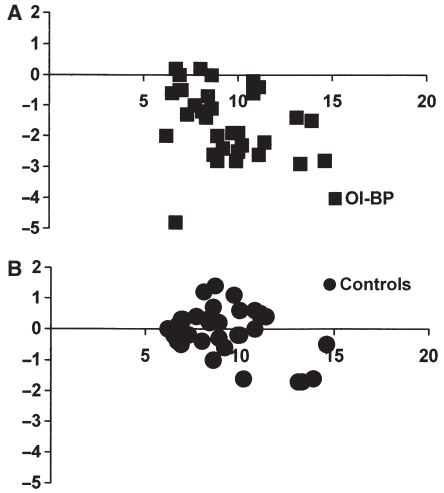

Fig. 1. Overview of the individual results for bisphosphonate-treated osteogenesis imperfecta (OI) patients (OI-BP) (A) and controls (B). Dental maturity was determined as the difference between calculated dental age (plotted on the *y*-axis) (see the text) and chronological age (plotted on the *x*-axis).

Discussion

For practical and ethical reasons, our study was based only on clinical examination of dental eruption status. Although various dental abnormalities are associated with OI, alterations of tooth eruption were not found to be prevalent in a previous study (9). The patients described in this previous study did not receive bisphosphonate therapy and only one of the 68 patients reported on had delayed tooth eruption. In this patient, only the lower medial incisor had erupted at 19 months of age, and at 30 months of age only eight teeth had erupted, although all expected teeth were visible on radiographs. Thirty-two patients in this study were between 5 and 14 yr of age and had age-appropriate tooth eruption (9). An earlier study involving about 40 patients reported similar findings (6). There is strong evidence in our study that bisphosphonate therapy is responsible for delayed teeth eruption. Moreover, the delay seems to be dose dependent and unrelated to the duration of treatment.

Table 1

Distribution of osteogenesis imperfecta patients and controls by number of delayed teeth

Number of delayed teeth	Controls	Bisphosphonate-treated OI patients				
		All patients	With DI	Without DI	Low dose of BP	High dose of BP
0	31	16	6	10	12	4
1	1	5	1	4	3	2
2	1	4	3	1	0	4
≥ 3	0	8	5	3	2	6

BP, bisphosphonates; DI, dentinogenesis imperfecta; OI, osteogenesis imperfecta.

An overall picture of the dentition, as assessed by analysis of tooth emergence, can only be obtained by counting emerged teeth in individuals during the period of eruption of the primary or permanent dentition (16). Various methods have been reported by many investigators (16, 18–20). In the present study, we only used a clinical analysis of tooth emergence. Tooth eruption is mediated by bone remodeling and dental development, which is contingent on further root development prior to the initiation of bone remodeling. Our clinical examination does not distinguish between bone remodeling and root development. Nevertheless, there is biological evidence to suggest that bisphosphonates have a direct effect only on the former mechanism (21).

The development of a tooth and its emergence into the oral cavity are complicated phenomena, and the mechanisms are not yet fully understood. Individual teeth develop within the jaws, and eruption occurs during a complex process involving bone remodeling on opposite sides of the developing teeth (21). In addition to bone changes, eruption of the permanent teeth necessitates resorption and exfoliation of the primary teeth. The requirement of alveolar bone resorption for tooth eruption was first noted in osteopetrotic rodents. Ostepetrosis is a congenital bone disease involving reduced bone resorption but not reduced bone formation (22), and in many cases there is failure of teeth eruption. For example, in the toothless rat (*tl*), the teeth are fully formed but do not erupt (23). Such animals have few osteoclasts, and they are probably non-functional (22, 24). This was confirmed by scanning electron microscopy showing the absence of bone resorption in the crypts of *tl* rats, contrasting with the scalloped crypt surfaces in normal rats, which indicate bone resorption. In another strain of osteopetrotic rats (*ia*) in which the teeth do not erupt, irradiation and injection of spleen cells from normal rats resulted in tooth eruption owing to the differentiation of functional osteoclasts (25). Also, osteopetrotic (*op*/*op*) mutant animals have fewer osteoclasts than normal mice, and their teeth do not erupt (26).

A direct causal relationship between resorption of alveolar bone by osteoclasts and tooth eruption has been shown in studies in which pamidronate, a bisphosphonate that reduces bone resorption by osteoclasts, was injected into rats (13). Eruption was delayed by 8 d for the first mandibular molars, by 1.6 d for the mandibular incisors, and by 2.5 d for the maxillary incisors. The cytological effect of this treatment was to increase the size of the osteoclasts and the number of nuclei, suggesting that the osteoclasts might be increasing in size to compensate for their reduced ability to resorb bone (13). It was also found (27) that both single and multiple injections of a bisphosphonate in rats inhibited the formation of acellular cementum in the teeth; a cellular hard tissue matrix was formed on the newly developed dentin surface, but not on previously formed acellular cementum. This hard tissue matrix was gradually resorbed after ending bisphosphonate treatment (28, 29).

Nitrogen-containing bisphosphonates (N-BPs) are currently used in the treatment of bone fragility in humans. The only previously reported effects of bisphosphonates on teeth are slight disruptions in the formation of enamel and dentine in rats (30). After internalization, N-BPs inhibit a key enzyme, farnesyldiphosphate synthase, in the biosynthetic mevalonate pathway (31, 32). As a result, N-BPs interfere with a variety of cellular functions essential for the bone-resorbing activity and survival of osteoclasts (33). Several intermediates in this pathway, including farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are required for the post-translational modification (i.e. prenylation) of guanosine triphosphate-binding proteins such as Ras, Rho, and Rac (34). These signaling molecules are involved in the regulation of cell proliferation, cell survival, and cytoskeletal organization (33). In particular, inhibition of protein prenylation and Ras signaling within osteoclasts leads to defects in intracellular vesicle transport (35). As a result, osteoclasts cannot form a tight-sealing zone or ruffled borders, which are required for bone resorption. These observations may explain the delayed tooth eruption observed in bisphosphonate-treated OI patients.

Our study has shown that bisphosphonate therapy delays tooth eruption in humans, consistent with its effects in rats. Bisphosphonates have a large effect on bone fragility in OI patients and delayed tooth eruption is a minor side-effect of this therapy. However, delayed tooth eruption should be considered, particularly as it may increase the number of impacted teeth in patients already suffering from dental disorders.

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