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Bisphosphonate Therapy in Children With Osteogenesis Imperfecta

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"At the present time, no agent is available which will be of any value to the practitioner who has a patient with osteogenesis imperfecta" J. A. Albright, 1981 (1).

Osteogenesis imperfecta (OI) has long been a source of frustration to clinical researchers. At a time when their colleagues from basic science identified collagen type I mutations as the most common cause of OI, medical doctors stood empty-handed when it came to improving the often extreme bone fragility caused by these mutations. They could do little more than refer such patients to physiotherapy, occupational therapy, and orthopedic surgery. The treatment modalities offered by these departments still form the backbone of OI therapy today, but medical treatment with bisphosphonates has taken center stage, at least as far as published clinical research in this small field is concerned. What has happened?

Intravenous Pamidronate: Short-Term Effects

The sea change from frustration to enthusiasm was brought about by a series of observational studies in which intravenous pamidronate was given to a few dozen children and adolescents with moderate to severe forms of OI (2-5). It was reported that intravenous pamidronate infusions, given every one to four months, led to a marked and rapid decrease of chronic bone pain, an increased sense of well-being, and a rapid rise in vertebral bone mineral mass. Collapsed vertebral bodies were also noted to regain a more normal shape (2-7).

Intravenous Pamidronate: Effects on Bone Tissue

Pamidronate treatment is one of a handful of pediatric therapies whose effectiveness has been evaluated in longitudinal bone histomorphometric analyses (8). These analyses showed a marked increase in cortical thickness. Trabecular bone volume increased to a lesser extent, which was the result of an increase in trabecular number, but not in trabecular thickness. The surprising action on cortical thickness can be explained by the effect of pamidronate on bone modeling, the process that determines cortical thickening during growth. In modeling, osteoblasts and osteoclasts are active on opposite sides of the cortex and thus are not directly coupled (9). When osteoclasts are inactivated by pamidronate, osteoblasts can therefore continue to form bone, leading to an increase in cortical thickness.

In contrast, trabecular thickness is determined by remodeling, not modeling. In this process, osteoblasts are directly coupled to osteoclasts. Inhibition of osteoclast action by pamidronate therefore leads to a similar decrease in osteoblast activity, apparently without change in the balance between resorption and formation. Consequently, trabecular thickness does not change. Similar observations have been made in adult osteoporosis patients who received alendronate (10).

The effect of pamidronate on trabecular number probably reflects the action of the drug on endochondral growth. During this process, most of the trabeculae that are

initially created at the growth plate-metaphysis interface are normally lost during the conversion of primary into secondary spongiosa. The antiresorptive action of pamidronate presumably allows the survival of more primary trabeculae, which then can become secondary trabeculae (11).

Thus, the main effects of pamidronate in children with OI seem to depend on interference of the drug with two growth-related processes, modeling and endochondral bone formation. This could explain why the effect of pamidronate on bone mass is much more marked in children than in adult OI patients (12).

Intravenous Pamidronate: Long-Term Effects

Although physicians caring for children with OI readily embraced intravenous pamidronate, scientific criticism of this treatment approach lingers (13,14). As is pointed out by critics, intravenous pamidronate in OI has not been subjected to the litmus test of clinical research, the randomized controlled trial. It is therefore not possible to formally distinguish the effects of the drug from those of other concomitantly applied treatments (*e.g.*, physiotherapy) or placebo effects. Yet, to many investigators, the initial clinical benefits of pamidronate, especially on bone pain and stamina, are so obvious that placebo infusions seem hard to justify.

The longer term effects of pamidronate infusions are less clear. In this regard, the lack of well-defined outcome parameters has been rightly criticized (13). Often, what we are actually trying to achieve with this treatment is not made sufficiently clear. On reviewing the literature, one comes away with the impression that lumbar spine bone mineral density (BMD) is the most important outcome parameter, because it is the single value that is invariably reported. However, increasing lumbar spine BMD could reflect not only the desired treatment effect (*e.g.*, thicker cortices or more cancellous bone), but also a side effect of antiresorptive treatment in children -- namely, the accumulation of mineralized growth plate cartilage remnants in bone tissue (8). In addition,lumbar spine BMD also increases when vertebrae collapse, which is a frequent occurrence in OI. Therefore, BMD measurements alone are not conclusive proof of treatment effectiveness, but must be buttressed by bone morphometry, both on the microscopic and macroscopic level (6-8).

Making bones heavier and improving their shape are important and encouraging achievements, but the ultimate goal of treatment should be to optimize the development of musculoskeletal function, rather than mass and shape, to achieve better mobility and improved performance in activities of daily living. It has not been established whether these goals have been achieved. In the two largest observational studies, improved mobility was reported in more than one-half of patients (3,15), but the proportion of untreated OI patients who will experience improved mobility without medical therapy remains unknown. In any case, mobility and other functional parameters are quite unlikely to improve with medical intervention alone, but critically depend on adequate orthopedic and rehabilitative support.

Intravenous Pamidronate: Side Effects

The short-term side effects of pamidronate in children with OI are usually limited to a “flu-like” reaction during the first infusion that can be accompanied by fever, rash, and vomiting (3,5,15). With regard to long-term safety, there was initially a great deal of concern regarding the effect on growth, given the well-known growth-suppressive effect of high-dose bisphosphonates in animals (16). Fortunately, no negative effect of pamidronate on growth has been detected in children with moderate to severe OI (5,15,17); however, pamidronate does suppress bone turnover well below age-specific reference ranges, which in the long run, could lead to an accumulation of microdamage in bone tissue or impair fracture repair (8). These possibilities must be closely monitored in ongoing clinical trials.

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More Open Questions

There is a long list of questions regarding bisphosphonate treatment in children with OI that have not been addressed, including the following: How long should pamidronate treatment be continued to optimize the benefits and minimize the potential for long-term side effects? Do other bisphosphonates have effects similar to pamidronate? Concerning this question, results from several controlled trials using oral bisphosphonates should be forthcoming in the near future. Do children with "mild" forms of OI (*i.e.*, those who have two or fewer fractures per year, no vertebral compression fractures, and no long bone deformities) benefit from bisphosphonate treatment at all? Results from studies on moderate to severe OI cannot be simply extrapolated to children with mild disorders, because such children have less to gain from therapy than do severely affected patients; however, they also have more to lose from potential adverse effects.

Conclusion

Pamidronate therapy has become the *de facto* standard of care for children and adolescents with moderate to severe OI, mainly because of its marked effects on bone pain, stamina, and BMD. Nevertheless, many questions regarding the long-term effects of pamidronate remain unanswered at the present time. Next to nothing is known about the effectiveness of other bisphosphonates in such patients. Whatever the exact long-term effects of bisphosphonates may turn out to be, it is clear that they do not constitute a cure for OI, but rather are an adjunct to physiotherapy, rehabilitation, and orthopedic care.

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