

EDITORIAL

Bisphosphonates in Childhood Rheumatic Disease-Have We Opened Pandora's Box??

Bisphosphonates have revolutionized the care of children with osteogenesis imperfecta (OI), a disease where frequent fractures debilitate a child. (1) What is the role of this class of medications in childhood rheumatic diseases? The article by Cimaz does an excellent job of summarizing the small uncontrolled trials of bisphosphonates in the pediatric rheumatic diseases; he recommends the use of this class of medications only in a research setting with long term follow up. Below is reviewed the mechanism of action of bisphosphonates along with the potential hazards of use in childhood.

Bisphosphonates are synthetic pyrophosphate analogs with replacement of the oxygen of the phosphate-oxygen-phosphate (P-O-P) skeleton with a carbon, P-C-P; this allows for the addition of two side chains to the carbon molecule. The biological action is in the two carbon side chains, referred to by R^1 and R^2 . The affinity for the hydroxyapatite bone mineral is the property of the R^1 side chain, and the biological activity on osteoclasts is dependent on the R^2 side chain. (2) The newer, more potent bisphosphonates, so called third generation bisphosphonates (e.g., alendronate, risedronate, zoledronate, ibandronate), have a nitrogen group as one of the side chains and are usually preferred over non-nitrogen side chain preparations (e.g., etidronate, clodronate, tiludronate). This preference is because of the increased potency of the nitrogen containing compounds. Bisphosphonates irreversibly bind and inactivate osteoclasts, and induce apoptosis of the osteoclast. In addition, they decrease osteoclasts recruitment, differentiation and action. Bisphosphonates work by inhibition of the mevalonate pathway, the pathway responsible for cholesterol synthesis. The inactivated osteoclast is then incorporated into the bone matrix. The half life of bisphosphonates in adults has been estimated to be greater than 10 years; after 10 years the amount of bisphosphonate released from the skeleton is estimated to be 25% of that absorbed from the GI tract with oral dosing. There have been no studies of bisphosphonates in children that have spanned 10 years.

The dosing of bisphosphonates varies by indication and formulation. There are intravenous formulations that may be given from monthly to yearly. The initial intermittent dosing regimen of pamidronate initially reported by Glorieux for treatment of OI was every 4 to 6 months. For post-menopausal osteoporosis oral medication dosing was initially daily, then weekly dosing regimens of bisphosphonates were found to be just as effective and easier to take. The trials of bisphosphonate use in glucocorticoid induced osteoporosis all used daily, not weekly dosing regimens. (3) Oral dosing is problematic in that the patient must take the medication first thing in the morning, on an empty stomach with water and remain upright without further drinking or eating for 30 minutes. This dosing regimen is recommended because in general bisphosphonates are

poorly absorbed from the GI tract, and taking the medication with food or other fluids decreases absorption. In addition, esophagitis is a well known side effect and taking the medication as directed decreases the potential for esophagitis.

Osteoclast function is essential for normal linear growth in childhood as well as the normal bone remodeling that occurs at all ages. It appears that linear growth remains normal, or at least still occurs, in children taking bisphosphonates; the mechanism of action of this phenomenon is unclear. It is well recognized that there are bands of sclerotic bone in the metaphyseal regions seen on plain radiographs of children taking bisphosphonates. For those that receive intermittent dosing (i.e.: every 3 months) there will be serial bands seen on radiographs corresponding to the time the growing bone has spent under the influence of the bisphosphonates. The clinical significance of these bands is unclear. In pre-pubertal children normalization of the shape of the vertebral bodies after radiographic compression fractures has been reported. (4) There is one report of bone biopsies performed at different times during a treatment regimen examining the bone architecture in 6 of 12 children on long term bisphosphonate therapy (2.2-7.8 years); the treatment regimens varied from daily oral to IV intermittent dosing. (4) All the children had an increase in their bone densitometry Z-scores over time. Results of the iliac crest bone biopsies in the selected children showed normal lamellar structure without mineralization defects. These results are certainly encouraging as far as pediatric use of these drugs.

There have been few studies of bisphosphonates in children, and no randomized placebo controlled studies. The wait for well designed, randomized, clinical trials in the treatment of childhood osteoporosis is overwhelming when one is faced with a child with a rheumatic disease, on corticosteroids, and now with back pain and a compression fracture on radiograph. Can we sit and do nothing? It goes against our training and compassion as pediatric rheumatologists. We are (unfortunately) used to treating diseases without evidence based medicine. Look, for example, at the lack of a single randomized trial in the treatment of juvenile dermatomyositis, or the treatment of systemic sclerosis of childhood. Certainly we cannot afford not to treat our patients with the best medicine collective wisdom has accumulated.

There are so many questions about bone epidemiology as it applies to children, especially in the rheumatic diseases. This starts with basic questions. What is a low bone mass in children? Is there a critical low densitometry Z-score we should be treating? Should all children starting chronic corticosteroids start calcium supplementation and vitamin D? Will this prevent osteoporosis in this population? When should we consider bisphosphonate therapy? Should we be treating low bone mineral density readings or only fractures? If we wait for fractures have we waited too long? Will we actually do damage to children in thirty or forty years because of bisphosphonate treatment? With so many unanswered questions and the potential for long term

complications, it behooves us to use attempt to answer these questions by performing collaborative trials and by collectively observing children long term looking at long term objective outcomes.

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REFERENCES

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