EFFICACY OF ALENDRONATE IN INFANT OIM/OIM MICE.

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The group of compounds known as bisphosphonates has been shown to decrease fracture risk in osteoporotic women (1) and more recently, in children with osteogenesis imperfecta (OI) (2). However, carefully controlled studies in animal models are required to fully characterize the quality and mechanical properties of the bone formed after treatment. To address this issue, the efficacy of the third-generation bisphosphonate alendronate was tested in the growing homozygous oim/oim mouse, a naturally occurring animal model of moderate to severe OI which is deficient in proalpha2 collagen (3).

Alendronate (generously supplied by Merck & Co) (26ug/kg/dose or 73 ug/kg/dose) was administered to nursing oim/oim mice pups starting at age 2 weeks through 6 weeks via alternate-day subcutaneous injection. Control oim/oim mice received an equal volume of normal saline. Mice were weighed before each injection and dose adjusted accordingly. After 4 weeks of treatment mice were euthanized, whole body AP and lateral radiographs were taken and digitized. The number of fractures was counted and Cobb angle cervical lordosis and thoracic kyphosis measured. Femora were dissected, radiographed with a step-wedge density standard, digitized, and analyzed with SigmaScan software (Jandel Scientific) for geometrical and bone mineral density changes.

The average number of fractures sustained by the treated mice during the 4 week treatment period was reduced compared to the non-treated oim/oim mice. At both doses the treated oim/oim mice sustained an average of 1.00 fractures per mouse as compared to an average of 2.16 fractures per mouse in the non-treated oim/oim mice. In addition, a dose-dependent trend toward decreased lordosis and kyphosis was observed. However, the treated mice exhibited reduced weight gain and long bone growth compared to non-treated oim/oim mice.

The pilot study demonstrates that alendronate may be effective in reducing fractures ad correcting spine curvature in an infant mouse model of OI, and by analogy in infants with OI. Future histological and mechanical studies on bone from the treated animals will provide additional insight into alendronate-related effects on bone. If early treatment results in improved strength and quality of bone for the young oim/oim mouse pups, it is likely that the quality of bone formed in infants and children with OI will be improved with alendronate therapy.

References:
1. Gloreiux et al., N Engl J Med. 1998 Oct (14):947
2. Chipman et al., PNAS U S A. 1993 Mar (5):1701
3. Ensrud et al., Arch Intern Med. 1997 (22):2617.

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