Differential effects of MPMBP, a novel non-nitrogen-containing bisphosphonate, and zoledronate on bone turnover in neonatal and growing rats

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Nitrogen-containing bisphosphonates, including pamidronate and zoledronate, have been successfully used to treat osteogenesis imperfecta and leukemia and to reduce the risk of fractures in children. The studies performed to date have examined the efficacy and safety of bisphosphonates in adults, and little is known about the adverse effects of these agents in the young population.

In this study, we compared the efficacy and safety of a newly developed non-nitrogen-containing bisphosphonate, [4-(methylthio)phenylthio] methanebisphosphonate (MPMBP) with those of zoledronate, a third-generation nitrogen-containing bisphosphonate, in neonatal and growing rats.

MPMBP (1.2, 2.4, or 6.0 mg/kg) or zoledronate (0.05 or 0.1 mg/kg) was injected subcutaneously every three days in neonatal rats (3 to 18 days) or in growing rats (3 to 6 weeks). The animals were killed after sequential labelling with tetracycline and calcein, and then, the tibias, femurs, jaw bones were harvested and examined. Compared to the saline-injected control rats, the growing rats in both the zoledronate- and MPMBP-treated groups showed a gradual increase in body weight. Bone morphometric analyses using X-ray micro-computed tomography showed that both bisphosphonates increased the bone mass and density of the distal femur and proximal tibia; these findings were consistent with those observed in our previous studies. The plasma levels of tartrate-resistant acid phosphatase decreased in both the zoledronate- and MPMBP-treated groups, which indicated that both bisphosphonates were effective in suppressing bone resorption and thus increasing the bone mass. The group of zoledronate-treated neonatal rats showed less body weight gain, suppression of longitudinal growth in the hind limbs, and a marked delay in tooth eruption, whereas the group of MPMBP (1.2 mg/kg)-treated rats showed normal weight gain and eruption of teeth at the appropriate developmental stage.

In conclusion, our results show that MPMBP has a potent anabolic action on bones and little adverse effects, whereas zoledronate has considerable adverse effects, including retardation in longitudinal growth and tooth eruption, likely because of excessive inhibition of bone resorption and/or bone turnover, which might limit the clinical use of this drug in children.