High dose long term pre-treatment with Pamidronate does not interfere with initial endochondral fracture union but reduces resorption dependent bone formation during the later stages of callus remodelling in a rat fracture model.

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Introduction

Current treatment strategies for the debilitating disease Osteogenesis Imperfecta focus on improving bone mass and quality by reducing bone turnover. This is achieved by the use of chronic high doses of a group of well known anti-resorptive agents, Bisphosphonates (BP’s). Such intervention has led to widespread success in the treatment of this diseased population, improving overall bone mass, which translates to increased strength and resistance to fracture. However, common concerns exist amongst clinicians administering these agents regarding the extensive reductions in bone formation seen after chronic BP therapy. Furthermore, the high incidence of fractures that occur prior to and during BP therapy has led to speculation that BP’s may be complicating the already compromised bone healing seen in these patients. This study aimed to examine the extent to which high dose medium term BP treatment can reduce bone formation and potentially complicate bone repair.

Hypothesis

High dose medium term PAM will reduce bone formation and interfere with initial endochondral fracture union

Methods

Closed femoral fractures were produced in 9 week old Wistar rats and PAM was administered subcutaneously at 0.15mg/kg, 0.5mg/kg and 5 mg/kg twice weekly, commencing 4 weeks prior to fracture. Eight rats were allocated to each group, as shown below. Calcein was administered over Saline with high dose PAM treatment (p<0.01).

Proximal left tibia were analyzed for systemic effects of the high PAM doses used.

QCT – Fracture Callus

Bone formation in initial union, 2 weeks post fracture, was not reduced with PAM treatment however the percent of labeled bone within the fracture callus was significantly reduced by 38%, 43% and 63% for low, medium and high dose PAM respectively (p<0.01, figure 1). The mineral apposition rate (MAR) within the calluses at 6 weeks was also significantly reduced by 32% with low dose PAM, 38% with medium PAM and 49% with high dose PAM treatment compared to Saline (p<0.01). Callus osteoclast number was significantly increased up to 2-fold with PAM treatment (p<0.01), however osteoclast surface per um bone surface was unchanged with treatment.

Discussion

Medium term high dose Pamidronate treatment did not interfere with the vital process of endochondral fracture union in this model, suggesting osteoclastic resorption is not essential to this process. Inhibition of callus remodelling with PAM treatment however led to large increases in callus bone content, size and moment of inertia. Bone formation to initial union, 2 weeks, was not reduced with PAM treatment although systemically endosteal MAR was reduced in these animals. By 6 weeks however, after the achievement of union, remodelling was inhibited with PAM treatment, leading to reduced callus formation. These results suggest that the initial anabolic drive towards union is not dependent on bone resorption, whereas at 6 weeks bone formation is driven by remodelling. This outcome is complimented by the notable decreases in endosteal bone formation and minimal changes in periosteal bone formation systemically.

References