

Geranylgeraniol, a Potential Therapeutic Agent for Reducing Osteonecrosis of the Jaw Events Following Oral Tissue Manipulation

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Problem: Osteonecrosis of the Jaws (ONJ) is a clinical condition that is characterized by a non-healing breach in the oral mucosa resulting in exposure of bone and has been reported in patients receiving bisphosphonate therapy. Despite much research, the pathogenesis of ONJ remains ill defined.

Hypothesis: Critical to oral wound healing are cellular differentiation, proliferation, and migration of oral fibroblasts. We propose that the addition of growth factors and metabolic intermediates should be able to reverse inhibitory effects in vitro.

Methods: Oral fibroblasts were isolated from discarded surgical tissue. Cellular proliferation was measured using a MTS/PMS reagent-based kit. Wound healing experiments were performed in 6 well plates. Cells were plated on glass coverslips coated with fibronectin for immunofluorescence experiments.

Results: Geranylgeraniol was able to rescue proliferation in fibroblasts treated with 0.03mM pamidronate and 0.008mM and 0.03mM zoledronate. 0.06mM pamidronate and 0.03mM zoledronate inhibited the ability of fibroblasts to close scratch wounds. In wound healing experiments, Geranylgeraniol was able to rescue 0.03mM zoledronate inhibited cells, but not cells treated with 0.06mM pamidronate. Cells treated with zoledronate had very little expression of vinculin compared with untreated cells. Geranylgeraniol was able to restore vinculin expression in zoledronate treated cells.

Conclusion: Geranylgeraniol acts as a metabolic intermediate analogue from which GTPases can be synthesized in the presence of bisphosphonates. We propose that bisphosphonate treatment causes a GTPase production decrease which results in the inability of oral fibroblasts to interact with extracellular matrix thus reducing proliferation and migration rates in vitro.