J Musculoskel Neuron Interact 2003; 3(4):314-316

Perspective Article

Hylonome

Fracture healing with anti-resorptive agents

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Keywords: Fracture Healing, Bisphosphonates, Raloxifene, Anti-resorptive Agents

Introduction

Anti-resorptive agents— bisphosphonates, estrogen, and selective estrogen receptor modulators (SERMs)— currently, are used widely for the treatment of osteoporosis in postmenopausal women[1-7]. However, inhibition of bone resorption secondarily suppresses bone formation activity[1,2,8], which results in a substantial reduction in bone turnover, as confirmed by 90% reduction in activation frequency after 2 years of alendronate treatment in women[9]. Different from other anti-resorptive agents, bisphosphonates have a high affinity for bone mineral and their skeletal half-life in bone is very long. For alendronate it is approximately 200 days in rats, 3 years in dogs and 12 years in humans[10]. Bone remodeling is considered to have an important physiologic function such as replacing old skeletal tissue to the new as well as calcium transport. Long retention of bisphosphonates in bone might result in a prolonged suppression of bone remodeling, thereby substantially inducing harmful effects in bone[11]. Because patients with osteoporosis are prone to fractures and because bisphosphonates, estrogen and SERMs suppress bone remodeling, we have investigated what effect they might have on the healing of fractures that might occur during treatment.

Part I - Fracture healing with incadronate disodium (YM-175)

Incadronate (YM-175, Yamanouchi, Japan) is one of the third generation bisphosphonates, similar to risedronates or alendronates. The fracture model of rat's femoral shaft was used in these studies. Female Sprague Dawley rats of 8 weeks old were injected s.c. with either vehicle (V group) or two doses of incadronate (10 μg/kg and 100 μg/kg) 3 times a week for 2 weeks, where 100μg/kg, 3 times a week, was 10 times that of the anticipated clinical therapeutic dosage. The right femoral diaphysis was then fractured and fixed with intramedullary stainless wire. Just after fracture, incadronate treatment was stopped in pre-treatment groups (P-groups: P-10 and P-100) or continued in continuous treatment groups (C-groups: C-10 and C-100). All rats were sacrificed at 2 or 4 weeks after surgery to see the early stage effect[12], at 6 or 16 weeks to see the middle stage effect[13], and at 25 or 49 weeks to see the long-term effect of the bisphosphonate on the fracture healing process[14].

Early stage effect (at 2 and 4 weeks post-fracture)

A significantly enlarged callus was observed only in the C-100 group compared with the control, at 4 weeks but not at 2 weeks. Both linear labeled surface and eroded surface decreased significantly in the C-10 and C-100 groups at 2 and 4 weeks. Osteoclast number decreased significantly in the C-10 and C-100 groups at 2 weeks, but increased slightly at 4 weeks. However, there was no significant difference in the above parameters in P-10 and P-100 groups at 4 weeks. Apoptotic osteoclasts were observed only in the C-100 group at 4 weeks. A time-course decrease in incadronate concentration was detected in P-10 and P-100 groups, while an increase was observed in the C-10 and C-100 groups. These findings suggest that: larger callus under incadronate treatment may result from the inhibition of bone resorption; histological characteristics of callus may be correlated with incadronate concentration; metabolism of incadronate in bone may be related to the rate of bone turnover.

Middle stage effect (at 6 and 16 weeks post-fracture)

Incadronate treatment led to a larger callus, especially in the C-100 group at both 6 and 16 weeks. The process of fracture healing in the pre-treatment groups was delayed at 6 weeks,

The author has no conflict of interest.

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Accepted 1 August 2003

but reached control levels thereafter and showed the same characteristics as in control at 16 weeks. Woven bony callus could still be seen in continuous treatment groups at 16 weeks. Mechanical study indicated that the ultimate load of the C-100 group was slightly higher than the other treatment groups and control. The results suggest that pre-treatment with incadronate did not affect fracture healing at 16 weeks after fracture. However, continuous incadronate treatment could lead to a larger callus, but it delayed the remodeling process during fracture healing, especially with high dose treatment.

Long-term effect (at 25 and 49 weeks post-fracture)

The fracture line disappeared in all groups. The cross-sectional area in the C-100 group was the biggest among all groups and, in the C-10 group was larger than that in the group at 25 weeks. The process of fracture healing was delayed under continuous treatment with incadronate as evidenced by the delay of both lamellar cortical shell formation and resolution of original cortex in the C-groups. Percent linear labeling perimeter, mineral apposition rate and bone formation rate in C-groups significantly decreased compared to the other groups, indicating that the callus remodeling was suppressed under continuous treatment, especially with high dosage. Mechanical study showed that the stiffness and ultimate load of fractured femur in the C-100 group were the highest among the groups at both 25 and 49 weeks. Long-term continuous treatment with incadronate delayed the process of fracture healing especially under high dose, but it did not impair the recovery of mechanical integrity of the fracture.

Part II - The effects of estrogen, raloxifene, and alendronate, on fracture healing in OVX rats[15]

Sprague Dawley rats at 3 months of age were either ovariectomized or sham-operated and divided into five groups: Sham control, ovariectomized control (OVX), estrogen (0.1 mg/kg, EE2), raloxifene (1.0 mg/kg, Rlx) and alendronate (0.01 mg/kg, Aln) groups. Treatment began immediately after the surgery. Four weeks post-ovariectomy, fracture surgery was performed in the same manner as in the Part I studies. Treatment was continued and fracture calluses were excised at 6 and 16 weeks post-fracture. At 6 weeks post-fracture, Aln and OVX had larger calluses than other groups. Sham and OVX had higher ultimate load than EE2 and Rlx, with Aln not different from either control. Aln calluses also contained more mineral (BMC) than all other groups. By 16 weeks post-fracture, OVX calluses were smaller than at 6 weeks, while the dimensions for Aln had not changed. Aln had higher BMC and ultimate load than OVX, EE2 and Rlx. EE2 and Rlx had similar biomechanical properties, which were similar to Sham. Interestingly, OVX and Aln animals were heavier than other groups at all time points; therefore ultimate load was normalized by body weight to show no significant differences in the strength of the whole callus between the groups at either 6 or 16 weeks post-fracture. However, Aln strongly suppressed remodeling of the callus, resulting in the highest content of woven bone, persistent visibility of the original fracture line, and lowest content of lamellar bone, compared to other groups. Therefore, the larger Aln callus appeared to be a remarkable, morphological adaptation to secure the fracture with inferior material. OVX-stimulated bone turnover resulted in the fastest progression of fracture repair that was most delayed with alendronate treatment, consistent with marked suppression of bone resorption and formation activity. Estrogen and raloxifene had similar effects that were generally similar to Sham, indicating that mild suppression of bone turnover with these agents has insignificant effects on the progression of fracture repair.

Discussion

The fracture healing, process includes various stages such as enchondral ossification, woven bone production, and callus remodeling to lamellar bone. During the fracture healing radiological union of the fracture occurs earlier than recovery of the mechanical strength and histological healing of the fracture in both animal models[13,16,17] and humans[18]. In order to evaluate the process of fracture healing, not only radiological but also histological and histomorphometrical examinations, as well as mechanical testing of the fractured bone, should be carried out. The healing of the fracture may be considered complete when it reaches 1) radiological disappearance of the fracture line, 2) histological restoration of anatomical architecture and 3) mechanical recovery of bone strength[19-21]. Clinically, restoration of mechanical integrity of the fracture is the most critical issue. In comparison of the effects of the anti-resorptive agents in this series using the rat model, the fracture healing was most quickly advanced in OVX, least advanced in the bisphophonates, which was characterized by the remains of the original cortex, remained woven bone in callus, and large callus area, but not impaired recovery of mechanical integrity of the fracture. These data indicate that the bisphosphonate treatment does not prevent initiation of fracture healing and formation of the callus, but continued use did significantly impede the process of callus remodeling, which may be correlated with bisphosphonate concentration in bone. Also, our data showed that continuous treatment leads to time-dependent accumulation of bisphosphonate in bone. The large volume and cross-sectional area of the bisphophonate callus appeared to be an adaptation that the bisphosphonate delay of woven bone remodeling into lamellar bone, which is structurally and mechanically superior to woven bone. In high dose treatment of incadronate the fracture healing had not yet been histologically completed at the end of the experiment (49 weeks post fracture). If clinically relevant, these animal data taken together suggest that cessation of bisphosphonate treatment may be prudent for women on therapy who sustain a non-vertebral fracture. In contrast, mild suppression of bone turnover with estrogen and raloxifene has insignificant effects on the progression of fracture repair.

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