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Original article

Effect of combined treatment with zoledronic acid and propranolol on mechanical strength in an rat model of disuse osteoporosis

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ABSTRACT

Objectives: A model that uses right hind-limb unloading of rats is used to study the consequences of skeletal unloading during various conditions like space flights and prolonged bed rest in elderly. This study was aimed to investigate the additive effects of antiresorptive agent zoledronic acid (ZOL), alone and in combination with propranolol (PRO) in a rat model of disuse osteoporosis.

Methods: In the present study, 3-month-old male Wistar rats had their right hind-limb immobilized (RHLI) for 10 weeks to induce osteopenia, then were randomized into four groups: (1) RHLI positive control, (2) RHLI plus ZOL (50 μg/kg, i.v. single dose), (3) RHLI plus PRO (0.1 mg/kg, s.c. 5 days per week), (4) RHLI plus PRO (0.1 mg/kg, s.c. 5 days per week) plus ZOL (50 μg/kg, i.v. single dose) for another 10 weeks. One group of non-immobilized rats was used as negative control. At the end of treatment, the femurs were removed and tested for bone porosity, bone mechanical properties, and bone dry and ash weight.

Results: With respect to improvement in the mechanical strength of the femoral midshaft, the combination treatment with ZOL plus PRO was more effective than ZOL or PRO monotherapy. Moreover, combination therapy using ZOL plus PRO was more effective in improving dry bone weight and preserved the cortical bone porosity better than monotherapy using ZOL or PRO in RHLI rats.

Conclusions: These data suggest that this combined treatment with ZOL plus PRO should be recommended for the treatment of disuse osteoporosis.

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Efeitos da terapia combinada com ácido zoledrônico e propranolol na resistência mecânica em um modelo de rato com osteoporose por desuso

Palavras-chave:
Osteoporose por desuso
Estudo com ratos
Ácido zoledrônico
Propranolol

RESUMO

Objetivos: Investigar os efeitos aditivos do agente antirreabsorção ácido zoledrônico (ZOL), isolado e em combinação ao propranolol (PRO), em um modelo de rato com osteoporose por desuso.

Métodos: Usou-se um modelo de pata traseira direita de rato privada de descarga de peso para estudar as consequências da falta de descarga de peso sobre o esqueleto durante várias condições, como missões espaciais e repouso prolongado no leito em idosos. Ratos Wistar machos de três meses de idade foram submetidos à imobilização da pata traseira direita (IPTD) por 10 semanas para induzir à osteopenia; em seguida, foram divididos aleatoriamente em quatro grupos: 1 – IPTD para controle positivo; 2 – IPTD mais ZOL (50 μg/kg, dose única intravenosa); 3 – IPTD mais PRO (0,1 mg/kg, via subcutnea, cinco dias na semana); 4 – IPTD mais PRO (0,1 mg/kg, via subcutnea, cinco dias na semana) mais ZOL (50 μg/kg, dose única intravenosa) por outras 10 semanas. Um grupo de ratos não imobilizados foi usado como controle negativo. No fim do tratamento, os fêmures foram removidos e testaram-se a porosidade do osso e suas propriedades mecnicas, além do peso seco e das cinzas do osso.

Resultados: No que diz respeito à melhoria da resistência mecnica da diáfise femoral média, a terapia combinada com ZOL mais PRO foi mais eficaz do que a monoterapia com ZOL ou PRO. Além disso, a terapia combinada com ZOL mais PRO foi mais eficaz na melhoria do peso seco do osso e preservou melhor a porosidade do osso cortical do que a monoterapia com ZOL ou PRO em ratos submetidos à imobilização da pata traseira direita.

Conclusões: Esses dados sugerem que a terapia combinada com ZOL mais PRO deve ser recomendada para o tratamento da osteoporose por desuso.

Introduction

Osteoporosis is a bone debilitating disease that causes nearly 9 million bone fractures each year.[1] Disuse (unloading) is one of the important causes of osteoporosis.[2] Mechanical loading is essential for the normal functioning of bone tissue. Immobilization results in imbalance of bone metabolism followed by rapid bone loss and impairment of bone mechanical function.[3] This immobilization-induced bone loss is caused by an increased bone resorption and a decreased bone formation. Disuse (unloading) osteoporosis occurs in patients with spinal cord injuries, patients confined to prolonged bed rest, and astronauts exposed to microgravity during space flight.[2] Microgravity induced osteoporosis poses a major threat to the astronaut's health. Microgravity leads to the unloading of the skeleton especially weight bearing bones.[3] Disuse osteoporosis not only increases the susceptibility to fractures in patients with spinal cord injuries and elderly requiring bed rest, but also threatens safety and health of astronauts during spaceflights. Therefore, it is very essential to find relevant countermeasures for disuse osteoporosis to reduce or prevent such bone loss.

Several animal models have been suggested for studying immobilization induced bone loss including neurectomy, tail suspension, plaster casting, and elastic bandaging. In this study, right hind-limb immobilization (RHLI) was achieved by a new procedure which was developed to avoid the problems caused by most widely used methods for the immobilization (e.g., plaster cast, bandaging or tail suspension) of rats. The smaller weight of the framework compared with a plaster cast kept the difficulty in movement and locomotion to a minimum, with a consequent minimal body weight loss throughout the period of immobilization. Moreover, no skin ulceration or foot swelling was found in the animals when the immobilization was removed. The immobilization procedure proposed was effective in producing long-term disuse in the hind-limbs of rats and is a good alternative to the traditional methods of immobilization.[2]

Zoledronic acid (ZOL) is a third generation nitrogen containing bisphosphonate that binds to hydroxyapatite with the highest affinity and inhibits osteoclasts with the highest potency of all licensed bisphosphonates.[4,5] Therefore, ZOL needs only to be injected once annually in patients, while still efficiently inhibiting osteoclastic activity and thereby reducing the risk of fracture.[6] Although anti-resorptive agents such as bisphosphonates are effective in reducing bone loss, they are not able to induce formation of a new one.[5]

Propranolol (PRO), a non-selective β-adrenergic antagonist, is now considered to be a potential drug under investigation for fracture healing and more specifically for osteoporosis therapy. In rat model of postmenopausal osteoporosis treatment with PRO improves bone properties by increasing bone formation and decreasing bone resorption.[7–10] Moreover, various preclinical studies have demonstrated that treatment by PRO mitigated the bone loss induced by unloading.[2,11,12] Furthermore, results of some prior epidemiological studies confirm the hypothesis that β-blockers use is associated with a decrease in fracture risk.[13–15] Combination therapy is now the subject of extensive investigation because, in some cases, it