



Original article

Histomorphometry of the organic matrix of the femur in ovariectomized rats treated with sodium alendronate[☆]



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ABSTRACT

Objective: To evaluate the effect of two different concentrations of sodium alendronate on the quantity of organic matrix in the femur of rats with estrogen suppression caused by ovariectomy.

Methods: Sixty-days-old Wistar rats (*Rattus norvegicus*) were subjected to bilateral laparotomy to remove the ovaries. The animals were divided into a control group, in which they only underwent laparotomy; an ovariectomized group (OVX); an ovariectomized group treated with 1 mg/kg of alendronate (OVX 1 mg); and an ovariectomized group treated with 2 mg/kg of alendronate (OVX 2 mg). The rats received alendronate twice a week for 90 days. The left femur was then removed, fixed and processed for embedding in paraffin. Semi-serial sections stained with hematoxylin and eosin were used to determine the area occupied by organic bone matrix, by means of image analysis software. The animals' weights were obtained at the beginning and end of the experiment.

Results: The ovariectomized animals and those treated with 1 mg/kg of alendronate presented significant increases in body weight ($p < 0.05$), in comparison with the control group. Histomorphometric analysis revealed that in the animals treated with 2 mg/kg of alendronate, the area (μm^2) occupied by organic matrix ($1,81,900 \pm 18,130$) was similar ($p > 0.05$) to that of the non-ovariectomized control animals ($2,04,800 \pm 9590$), which indicates that this medication had a preventive effect with regard to bone mass loss.

Conclusion: The higher concentration of the medication, administered twice a week for 90 days, was more effective than the dose of 1 mg/kg over the same period.

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Histomorfometria da matriz orgânica do fêmur de ratas ovariectomizadas tratadas com alendronato de sódio

R E S U M O

Palavras-chave:

Ovariectomia
Alendronato
Osteoporose
Matriz óssea

Objetivo: Avaliar a efeito de duas concentrações diferentes de alendronato de sódio (ALN) sobre a quantidade de matriz orgânica no fêmur de ratas com supressão estrogênica provocada por ovariectomia.

Métodos: Ratas Wistar (*Rattus norvegicus*) com 60 dias foram submetidas a laparotomia bilateral para remoção dos ovários. Os animais foram divididos em grupo controle, no qual os animais foram apenas laparotomizados; grupo ovariectomizado (OVX); grupo ovariectomizado tratado com 1 mg/kg de ALN (OVX 1 mg); e grupo ovariectomizado tratado com 2 mg/kg de ALN (OVX 2 mg). Receberam ALN duas vezes por semana durante 90 dias. O fêmur esquerdo foi coletado, fixado e processado para inclusão em parafina. Cortes semisseriados corados com H&E foram usados para a obtenção, com um software de análise de imagens, da área ocupada por matriz óssea orgânica. O peso dos animais foi obtido no início e no fim do experimento.

Resultados: Os animais ovariectomizados e aqueles tratados com 1 mg/kg de ALN tiveram um aumento significativo ($p < 0,05$) no peso corporal quando comparados com o grupo controle. A análise histomorfométrica revelou que nos animais tratados com 2 mg/kg de ALN a área (μm^2) ocupada por matriz orgânica (181.900 ± 18.130) foi semelhante ($p > 0,05$) àquela dos animais controle não ovariectomizados (204.800 ± 9.590), o que indica um efeito preventivo desse medicamento sobre a perda de massa óssea.

Conclusão: A maior concentração do medicamento administrado duas vezes por semana por 90 dias foi mais eficaz do que a dose de 1 mg/kg no mesmo período.

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Introduction

Postmenopausal osteoporosis is a disease characterized by deterioration of the microarchitecture and reduction of bone mass as a function of increased reabsorption by osteoclasts, with consequently greater susceptibility to fractures. This condition has very high prevalence and occurs more frequently than the sum of cases of myocardial infarct, breast cancer and stroke.¹ Osteoporosis should be considered to be a public health problem,² because it affects individuals with regard to their social, physical and work functions and, therefore has a socioeconomic impact.³ The main cause of loss of bone mass among women is the estrogen deficiency that arises at the menopause.⁴

Over the last decade, bisphosphonates have become the cornerstone of osteoporosis treatment.⁵ They are used for treating and preventing this disease and oncological diseases that result in increased bone remodeling.⁶ Bisphosphonates have a chemical structure that has a strong affinity with calcium phosphate, which facilitates bonding to bone. During bone reabsorption,⁷ the drug is absorbed by the osteoclasts and causes rupture of the cytoskeleton, loss of the pleated border, inhibition of lysosomal enzymes, loss of reabsorptive activity and death due to apoptosis.⁸ Thus, there is a diminution of osteoclastic activity, without direct interference with neof ormation activity.⁹

Sodium alendronate (ALN) is a second-generation amino-bisphosphonate that is a potent inhibitor of osteoclastic reabsorption.¹⁰ Use of ALN suppresses bone remodeling^{11,12}

and increases bone mineral density (BMD), thereby contributing toward avoiding vertebral and non-vertebral fractures. Through using ALN, bone turnover markers present lower levels.¹² Use of a specific ALN dose for treating osteoporosis results in significant deceleration of disease progression.⁸

The animal model most used for studying postmenopausal osteoporosis comprises ovariectomy, because over a relatively short period after ovariectomy, a state of osteopenia very similar to the human condition is obtained.^{13,14} By using animals, it is also possible to investigate the different forms of treatment and medications that exist on the market. However, there is no consensus regarding the appropriate dose for tests on animals. The aim of this study was to evaluate the bone tissue response in ovariectomized rats, to two different concentrations of ALN, which is one of the most widely available drugs on the market for osteoporosis treatment.

Materials and methods

All the procedures were approved by the Ethics Committee for Animal Experimentation of the State University of Maringá (protocol no. 033/2009).

Experimental procedure

Female Wistar rats (*Rattus norvegicus*) of 60 days of age were anesthetized with an intramuscular injection of 2-(2,6 xylidine)-5,6-dihydro-4H-1,3-thiazine hydrochloride (Ronpun[®]) and ketamine hydrochloride (Ketalar[®]) in a 1:1

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