REVISTA BRASILEIRA DE REUMATOLOGIA

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SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Original article

Additive effects of zoledronic acid and propranolol on bone density and biochemical markers of bone turnover in osteopenic ovariectomized rats

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ARTICLE INFO

Article history:
Received 1 May 2014
Accepted 21 September 2014
Available online 6 January 2015

Keywords:
Rat model
Postmenopausal osteoporosis
Zoledronic acid
Propranolol

ABSTRACT

Objectives: The present study was designed to investigate further the efficacy and safety of zoledronic acid (ZOL) and propranolol (PRO) as monotherapy and combination therapy in a rat model of postmenopausal osteoporosis.
Methods: Female Wistar rats were ovariectomized (OVX) or sham-operated at 3 months of age. Twelve weeks post-surgery, rats were randomized into six groups: (1) sham + vehicle; (2) OVX + vehicle; (3) OVX + ZOL (100 μg/kg, i.v. single dose); (4) OVX + ZOL (50 μg/kg, i.v. single dose); (5) OVX + PRO (0.1 mg/kg, s.c. 5 days per week); (6) OVX + ZOL (50 μg/kg, i.v. single dose) + PRO (0.1 mg/kg, s.c. 5 days per week) for 12 weeks. After treatment, femurs were tested for bone density, porosity and trabecular micro-architecture. Biochemical markers in serum and urine were also determined.
Results: Combined treatment with ZOL plus PRO corrected the decrease in serum calcium and increase in serum alkaline phosphatase and tartarate resistant acid phosphatase level better than single-drug therapy using ZOL or PRO. Moreover, combined treatment with ZOL plus PRO corrected the increase in urine calcium, phosphorous and creatinine level better than single-drug therapy using ZOL or PRO. Combination therapy using ZOL plus PRO also preserved the trabecular micro-architecture and cortical bone porosity.
Conclusion: These data suggest that combined treatment with ZOL plus PRO could be a more effective approach for treating severe osteoporosis in humans.

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http://dx.doi.org/10.1016/j.rbre.2014.09.008

Efeitos combinados do ácido zoledrônico e do propranolol sobre a densidade óssea e marcadores bioquímicos de remodelação óssea em ratas osteopênicas submetidas à ovariectomia

Palavras-chave:
Estudo com ratos
Osteoporose pós-menopáusica
Ácido zoledrônico
Propranolol

RESUMO

Objetivos: Este estudo foi desenvolvido para investigar a eficácia e a segurança do ácido zoledrônico (ZOL) e do propranolol (PRO) como monoterapia e terapia combinada em um modelo de rato com osteoporose pós-menopáusica.
Métodos: Ratas Wistar fêmeas foram ovariectomizadas (OVX) ou submetidas à cirurgia simulada (placebo) aos três meses de idade. Doze semanas depois da cirurgia, as ratas foram divididas em seis grupos: (1) placebo + veículo; (2) OVX + veículo; (3) OVX + ZOL (100 μg/kg, dose única intravenosa); (4) OVX + ZOL (50 μg/kg, dose única intravenosa); (5) OVX + PRO (0,1 mg/kg, via subcutânea, cinco dias por semana); (6) OVX + ZOL (50 μg/kg, dose única intravenosa) + PRO (0,1 mg/kg, via subcutânea, cinco dias por semana) durante 12 semanas. Depois do tratamento, testou-se a densidade óssea, a porosidade e a microarquitetura trabecular dos fêmures. Também foram avaliados marcadores bioquímicos séricos e urinários.
Resultados: A terapia combinada com ZOL mais PRO foi mais eficaz em corrigir a diminuição do cálcio sérico e o aumento do nível sérico de fosfatase alcalina e fosfatase ácida resistente ao tartarato do que a monoterapia com ZOL ou PRO. Além disso, a terapia combinada com ZOL mais PRO foi mais eficaz em corrigir o aumento dos níveis urinários de cálcio, fósforo e creatinina do que a monoterapia com ZOL ou PRO. A terapia combinada com ZOL mais PRO também preservou a microarquitetura trabecular e a porosidade do osso cortical.
Conclusão: Os resultados sugerem que a terapia combinada com ZOL mais PRO pode ser a abordagem mais eficaz para o tratamento da osteoporose grave em humanos.

Introduction

Osteoporosis is a degenerative disease characterized by reduced bone mass and deterioration of bone microstructures which increases the risk of fracture.[1] Osteoporosis in most cases develops without symptoms and has a progressive course. Timely diagnosis and the selection of ideal therapy at the appropriate stages of the disease are essential for the effective treatment and prevention of osteoporosis.

Biochemical markers are emerging as one of the critical diagnostic tools to screen the bone remodeling during the progression of bone diseases. They are liberated into serum and urine as a result of bone formation and bone resorption and offer an overview of the skeletal health. Apart from invasive imaging techniques, biochemical markers are very effective tools for the estimation and are indicative of various metabolic bone disorders. In contrast to invasive methods like bone mechanical testing's, the biochemical markers are convenient to use, inexpensive and non-invasive, when tested and analyzed correctly, proves to be a potential tool for the diagnostic and therapeutic determination of bone disorders.[2,3]

Zoledronic acid (ZOL) is a third generation nitrogen containing bisphosphonate that has been shown to significantly reduce the risk of fractures in patients who receive the once-yearly dosing regimen for the treatment of postmenopausal osteoporosis.[4] Although anti-resorptive agents such as bisphosphonates are effective in reducing bone loss, they are not able to induce formation of new bone.[1]

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 an animal study, a lower dose of PRO, a nonselective β-blocker, has been shown to increase bone mass in different experimental models of bone disorders.[4–10] Results of some prior epidemiological studies confirm the hypothesis that β-blockers use is associated with a decrease in fracture risk.[11–13] Rodrigues et al., demonstrated that PRO suppress bone resorption by inhibiting osteoclastogenesis as well as inflammatory markers.[14] This result is supported by a previous finding, which showed that propranolol stimulates osteoprotegerin (OPG) on its own in osteoblast cells.[15] The ability to stimulate osteoblast, while also damping osteoclasts makes PRO an attractive and unique alternative to antiresorptive therapy for osteoporosis. PRO, which could directly prevent bone loss and biomechanical alteration by increasing bone formation and decreasing bone resorption, may be the next anabolic agent for osteoporosis treatment.[4,5,14,15]

Combinations of anabolic and antiresorptive agents have potential to improve bone density and bone strength more than either agent alone.[16] As ovariectomy-induced bone loss involves both increased bone resorption and decreased bone formation, it seems obvious to target the ovariectomy-induced bone loss with a combined anti-resorptive and bone anabolic treatment regimen, such as ZOL and PRO. We have previously shown that the combined ZOL and PRO therapy can improve the mechanical properties of the spine and femur and preserves the trabecular microarchitecture in a rat model of postmenopausal osteoporosis.[4] In the light of these results,