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Preservation of Phenytoin and Sodium Valproate Induced Bone Loss by Raloxifene through Modulating Serum Estradiol and TGF-β3 Content in Bone of Female Mice

Authors : Divya Vohora, Md. Jamir Anwar

Abstract : Antiepileptic drugs (AEDs)-induced adverse consequences on bone are now well recognized. Despite this, there is limited data on the effect of anti-osteoporotic therapies on AEDs-induced bone loss. Both phenytoin (PHT) and sodium valproate (SVP) inhibit human aromatase enzyme and stimulate microsomal catabolism of oestrogens. Estrogen deficiency states are known to reduce the deposition of transforming growth factor-β (TGF-β3), a bone matrix protein, having anti-osteoclastic property. Thus, an attempt was made to investigate the effect of raloxifene, a selective oestrogen receptor modulator, in comparison with CVD supplementation, on PHT and SVP-induced alterations in bone in mice. Further, the effect of raloxifene on seizures and on the antiepileptic efficacy of AEDs was also investigated. Swiss strains of female mice were treated with PHT (35 mg/kg, p.o.) and SVP (300 mg/kg, p.o.) for 120 days to induce bone loss as evidenced by reduced bone mineral density (BMD) and altered bone turnover markers in lumbar bones (alkaline phosphatase, tartarate resistant acid phosphatase, hydroxyproline) and urine (calcium). The bone loss was accompanied by reduced serum estradiol levels and bone TGF-β3 content. Preventive and curative treatment with raloxifene ameliorated bony alterations and was more effective than CVD. Deprived estrogen levels (that in turn reduced lumbar TGF-β3 content) following PHT and SVP, thus, might represent one of the various mechanisms of AEDs-induced bone loss. Raloxifene preserved the bony changes without interfering with their antiepileptic efficacy, and hence raloxifene could be a potential therapeutic option in the management of PHT and SVP-induced bone disease if clinically approved.

Keywords : antiepileptic drugs, osteoporosis, raloxifene, TGF-β3
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