Valproic Acid Induced Osteopenia and Its Prevention with Alfacalcidol and Alendronate.

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The present study was undertaken to investigate the effects of long term administration of valproate that is commonly used in clinics and co-administration of alfacalcidol or alendronate with valproate on bone metabolism in growing rats. Bone mineral densities and serum bone makers were determined. The samples obtained from tibial metaphysis were then prepared for histological observation. As the results, valproate decreased the bone mineral density in both metaphysis and diaphysis with dose dependent manner. The magnitude of the decrease was greater in the diaphysis than metaphysis. Decreased bone volume was observed in all of groups treated with valproate. Although the levels of serum calcium were not affected, valproate increased the activities of acid phosphatase and alkaline phosphatase in the serum. The above results showed that valproate could induce bone loss in growing rats. Possible reason of the decrease was due to bone loss. Combined administration of alfacalcidol or alendronete prevented the osteopnenia induced by valproate. Therefore, these drugs cloud have useful efficacy to prevent osteopenia induced by valproate.

Key words: osteopenia, bone metabolism, bone mineral density

Introduction

Long-term treatment with antiepileptics has been known to cause a variety of bone disorders. It was reported that long-term administration of phenytoin or zonisamide induce osteopenia in growing rats1,2). Thus, the present study was undertaken to investigate the effect of long termed administration of valproate that is used commonly in clinics on bone metabolism. In addition, co-administration of alfacalcidol or alendronate with valproate also investigated whether these agents have preventive effect against valproate-induced osteopenia in growing rats.

Materials and Methods

Experiment I : Male Wistar rats weighing 70 ± 5 g were used. Each group consisted of 10-11 animals. These groups received the following drug schedule for 5 weeks. (a) saline (vehicle for valproate); (b) 100 mg/kg sodium valproate; (c) 200 mg/kg sodium valproate; (d) 400 mg/kg sodium valproate. Under pentobarbital anesthesia, the tibiae were dissected and fixed in Karnovsky solution. After removing the adhesive soft tissues, soft X-ray microradiographs of the bones were taken and each BMD was determined by analyzing the grey levels of the target area in microradiographs with an image analyzer (Aspect, Mitani Corp., Fukui, Japan). The measured area is tibial metaphysis. After determination of bone mineral density, the tibial metaphyses were excised for histological observations. Sections were cut frontally at a thickness of 6 mm and stained with H-E for observation under a light microscope for changes in trabecular bone.

Experiment II: Male Wistar rats weighing 70 ± 5 g were used and were divided into following groups. (A) vehicle; (B) 150mg/kg per day sodium valproate; (C) 150mg/kg per day sodium valproate plus 0.1 μg/kg per day alfacalcidol; (D) 150 mg/kg per day sodium valproate plus 56μg/kg per week alendronate. (E) 150 mg/kg per day sodium valproate plus 0.1 μg/kg per day alfacalcidol plus 56μg/kg per week alendronate; (F) 0.1 μg/kg per day alfacalcidol; (G) 56μg/kg per week alendronate; (H) 0.1 μg/kg per day alfacalcidol plus 56ƒμg/kg per week alendronate. Bone mineral density was determined the method mentioned above. Serum bone makers were determined by commercially available kits.

Results

Experiment I : Five weeks after treatment, administration of valproate denreased bone mineral density in dose dependent manner. At a dose of 200 mg/kg valproiate bone mineral density of tibial metaphysic and diaphysis were decreased significantly. The magnitude of decrease was grater in the diaphysis ratherdecrease than in the metaohysis. A similar distribution of osteoid was observed. In brief, there were no evidences of rickets or osteomalacia.

Experiment II: After constant treatment of valproate for 5 weeks, trabecular bone in valproate treated group were decreased compared to vehicle treated groups. Although the levels of serum calcium were not affected, valproate increased the activities of acid phosphatase and alkaline phosphatase in the serum. Co-administration of alfacalcidol or alendronate with valpoate did not induce osteopenia.

Discussion

As the results, sodium valproate decreased the bone mineral density in both metaphysis and diaphysis. Decreased trabecular bone volume was also observed, but the symptom of rickets was not observed. Since osteoid accumulation were not observed, vitamin D deficiency was unlikely to play a critical role in decreasing bone mineral density it in the experimental conditions. Increase the activities of acid phosphatase and alkaline phosphatase in the serum suggested that valproate accelerated both bone resorption and formation. Co-administration of alfacalcidol or alendronate showed preventive efficacy against the osteopenia. On the other hand, however, decrease of bone mineral density was observed even in the valproate plus alendronate group compared with only alendronate group. This fact indicated that valproate induced osteopenia was not prevented completely only

by inhibiting bone resorption supporting the hypothesis mentioned above. Anyway, these two drugs (alfacalcidol and alendronate) cloud have useful efficacy for the therapy for the patient receiving chronic administration of valproate.

References

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