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Effect of omeprazole, pantoprazole and famotidine on rat bones

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Abstract

Background:

Osteoporosis is the most common age-related skeletal chronic disorder. The use of acid-suppressive drugs (especially: proton pump inhibitors; PPIs and H2 receptor blockers; H2RAs) is widespread in osteoporotic patients. to counteract inflammation and ulceration of esophagus and stomach caused by prolonged use of anti-resorptive medications bisphosphonates especially fracture risk While, others have not observed any fracture risk with the use of PPIs . The data on the effects of H2RAs are conflicting too.

These drugs can reduce gastric acid secretion by up to 98% , irreversibly deactivating the proton pump (H+/K+ ATPase) of the gastric parietal cells. H2RAs (cimetidine, ranitidine, famotidine) competitively inhibit H2 receptors, have similar effects to PPIs, although they are less potent, blocking only 70% of gastric acid production . It has been suggested a possible association between gastric acid suppressants and increased hip, spine, and any-site fractures risk has been found in previous studies. Several mechanisms of this association have been proposed in theory, such as the possibility that PPIs decrease calcium-absorption, leading to bone mineral density (BMD) loss or they decrease magnesium absorption, which is important to bone health, other studies suggest that these agents can cause hyperparathyroidism by acid suppression and lead to decrease in BMD.

Aim:

It was aimed to clarify the possible effects of chronic use of omeprazole, pantoprazole (PPIs) and famotidine (H2 receptor antagonist) on adult and old female rat bones.

Materials and Methods:

Forty eight (48) female Sprague–Dawley rats were used in this study, they were divided into two main groups, and each consisted of 24 rats: group A: are adult age rats (7-week old), group B: are old age rats (7-month old). Each main group was subdivided into four subgroups: omeprazole, pantoprazole, famotidine treated, and control subgroups. These drugs were given daily for successive 3 months by oral gavage. At the end of this study, blood was collected for measurement of serum calcium, alkaline phosphatase, estradiol, and osteocalcin levels. Femurs were collected and processed for hematoxylin and eosin (H&E) staining then examined under light microscope.

This study used forty eight (48) female Sprague–Dawley rats , 24 of them are the adult (7 week old, each of them weighing 120-150 g), the other 24 are old (7 month old, each of them weighing 250-300 g). Animals were obtained from the Medical Experimental Research Center (MERC) at Mansoura Faculty of Medicine; they were put in similar optimum housing conditions with free access to food and water. Animals were kept in cages at a room with controlled all experimental procedures. Rats were randomly divided into 8 groups (n=6 per group). Group

(A) represents adult rats, Group (B) represent old age rats.

Each main group was subdivided into four subgroups. Control subgroups in which rats were given oral carboxy methylcellulose, Omeprazole treated subgroups. rats received omeprazole at a dose of 10 mg/kg of body weight per day Pantoprazole treated subgroups. rats received pantoprazole at a dose of 3 mg/kg of body weight per day. Famotidine treated groups. Rats received famotidine at a dose of 3 mg/kg of body weight per day.

Samples collection:

At the end of the experimental period, animals were sacrificed (thiopental 50mg/kg). The blood was collected from carotid arteries. the clear sera were stored at –20°C until measurement of serum calcium, alkaline phosphatase, estradiol, and osteocalcin levels. . Femurs were collected and processed for histopathological examination.

Serum measurements:

Calcium level was measured by calcium colorimetric kits. Alkaline phosphatase level was measured by alkaline phosphatase kits. Estradiol (E2) level was determined by Estradiol ELISA kits. Rat osteocalcin ELISA kits were used in this study for measurement of serum osteocalcin level.

Bone histomorphometrical analysis of femurus bone:

The bone specimens were taken after routine histological handling. Sections from the metaphysis and the diaphysis of the femurs were processed for hematoxylin and eosin staining (H/E) and viewed under the light microscope. Osteoporosis changes in the bones were graded from 0 to 3. Grade 0. Bone with normal structure, Grade 1. Slight osteoporosis, bone showed early osteoporosis, namely osteocytic activation (hypertrophy of osteocytes and enlargement of their lacunae) and hypertrophy of endosteal cells, Grade 2. Moderate osteoporosis, beside the above changes, appearance of resorption cavities were in the compact bone, Grade 3. Severe osteoporosis, many resorption cavities were in the diaphysis with the larger cavities containing bone marrow spaces and the compact bone became significantly thinner and the image analysis procedure was done for cortical and trabecular bone thickness .

Results:

In the present study, omeprazole or pantoprazole administration to either adult or old female rats produced bone loss that is explained biochemically (low serum calcium, elevated alkaline phosphatase, and osteocalcin levels) and histologically (decrease in cortical and trabecular bone thickness, enlarged bone marrow spaces filled with fat tissue, and appearance of resorption cavities). In addition, these drugs have no effect

on serum estradiol level. The effects of these drugs on bone tissue were more prominent in old rats and pantoprazole produce significant changes more than omeprazole. On the other hand, famotidine administration produced bone changes only in old rats but less than omeprazole and pantoprazole.

Conclusions:

Omeprazole or pantoprazole administration induced bone lesions that were confirmed by a significant biochemical and histopathological changes (pantoprazole produced greater changes more than omeprazole). These bone changes were more prominent in old age. Also, Famotidine administration produced bone changes only in old age. The effect of these drugs on bone tissue was explained by calcium deficiency that occurs after prolonged period of gastric acid suppression and needs potent inhibitors of gastric acid secretion to occur.