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PHARMACOLOGY

BONE REMODELING AFTER ADMINISTRATION OF PROTON PUMP (H^+/K^+-ATPase) INHIBITORS AND ALENDRONATE IN OVARIECTOMIZED RATS

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Abstract: During osteoporosis therapy with alendronate, esophagitis and stomach ulceration may occur, requiring the concurrent use of drugs which decrease gastric juice production. The aim of the present study was to investigate the effect of concurrent administration of proton pump (H^+/K^+ATP-ase) inhibitors: omeprazole or pantoprazole and alendronate on bone remodeling in ovariectomized rats. The experiments were carried out on 3-month-old Wistar rats, divided into following groups (n = 8–10): NOVX – non-ovariectomized control rats; OVX – ovariectomized control rats; OVX + alendronate; OVX + omeprazole; OVX + omeprazole + alendronate; OVX + pantoprazole; OVX + pantoprazole + alendronate. The drugs were administered for 28 days: alendronate (3 mg/kg *p.o.*), omeprazole or pantoprazole (3 mg/kg *i.p.*). Bone remodeling was estimated based on histomorphometric evaluation of the tibia (endosteal and periosteal transverse growth and the osteoid width, transverse cross-section surface of the diaphysis and of the marrow cavity) and the femur (width of trabeculae in the distal epiphysis and metaphysis). Bone mass/100 g body mass and mass of bone mineral/100 mg bone mass in the tibia and femur were also determined. Pantoprazole stronger than omeprazole intensified bone remodeling disorders caused by estrogen deficiency in ovariectomized rats. Bone remodeling disorders were the result of intensification of bone resorption with concurrent inhibition of bone formation and mineralization. Pantoprazole, and to lesser extent omeprazole, weakened the preventive effect of alendronate on bone remodeling in ovariectomized rats.

Key words: omeprazole, pantoprazole, alendronate, osteoporosis

Estrogen deficiency in experimental model of bilateral ovariectomy in rats, likewise in women after menopause, causes increased bone remodeling rate with insufficient bone formation response to the increased resorption. Those changes lead to bone mass loss and the development of osteoporosis (1–7).

In postmenopausal osteoporosis treatment, alendronate (an aminobisphosphonate) is often used. This drug inhibits resorption processes and shifts the metabolic turnover balance to the advantage of bone formation (8). The antiresorptive effect of alendronate is a result of inhibition of farnesyl diphosphate synthase activity in the mevalonate pathway, which leads to decreased synthesis of farnesyl diphosphate and geranylgeranyl diphosphate, necessary for prenylation of small GTPases such as Rac, Rho and Rab. Lack of prenylation causes loss of osteoclast resorptive properties (8–10).

Prolonged use of alendronate in osteoporosis therapy may cause inflammation and ulceration of esophagus and stomach. Reduction of adverse effects of alendronate may be obtained by concurrent use of drugs decreasing hydrochloric acid production. Drugs which powerfully and long-term inhibit the production of hydrochloric acid by parietal cells of the stomach are inhibitors of the proton pump (H^+/K^+-ATPase) responsible for the potassium ion transport to the inside of the parietal cell and secretion of hydrogen ions to the stomach lumen (11). Omeprazole or pantoprazole are the most often used H^+/K^+-ATPase inhibitors. Those are the prodrugs, which are activated in acidic environment (pH approx. 1.0) of the tubules leading out the

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hydrochloric acid from parietal cells. An inactive inhibitor affected by hydrogen ions undergoes protonation into cyclic sulfenamid, which has the ability to create a covalent bond with free cysteine sulfhydryl groups of H^+/K^+-ATPase, causing its deactivation (12–15). The bond of the active metabolite with the enzyme is irreversible, and inhibition of hydrochloric acid secretion in the stomach remains until new H^+/K^+-ATPase molecules are synthesized and built in the cellular membrane of the secretory tubules of parietal cells. The effect of such activity is inhibition of hydrochloric acid secretion lasting for about 24–48 h, which is much longer than the half-life of the pro-drug in plasma (approx. 1.5–2 h) (12).

In the ruffled border of osteoclasts, there is a proton pump (H^+-ATPase), so-called V-ATPase, controlling intracellular and extracellular pH, which is extremely important for resorption processes (16). V-ATPase is built of a transmembrane domain V_o, which forms an ionic canal, and a cytoplasmic catalytic domain V_1 comprising of 8 subunits (A–H). Due to the occurrence of different isoforms of A and B subunits in the catalytic domain, V-ATPase may be sensitive not only to the inhibitors specific for that pump, but also to the inhibitors of H^+/K^+-ATPase which occurs in parietal cells of the stomach (17, 18).

Until now, the reports on effects of H^+/K^+-ATPase inhibitors on the skeletal system has been contradictory (19–22), whereas the effect of their concurrent administering along with bisphosphonates on the bone tissue remodeling in estrogen deficiency conditions has never been reported.

The aim of the present study was to examine the effect of omeprazole or pantoprazole and alendronate on bone remodeling processes in rats with estrogen deficiency caused by bilateral ovariectomy.

EXPERIMENTAL

The study was performed with consent of the Local Ethics Committee in Katowice, on 60 3-month-old female Wistar rats of initial body mass 210–240 g. In 50 females, in general anesthesia induced by intraperitoneal injections (*i.p.*) of ketamine (Biokethan) with xylazine (Rometar), bilateral ovariectomy procedure with access to the ovaries from the dorsal side was carried out (23). After 7 days, rats were divided into 7 groups (n = 8–10): control non-ovariectomized rats (NOVX), control ovariectomized rats (OVX), ovariectomized rats receiving: alendronate (OVX + A), omeprazole (OVX + O), omeprazole and alendronate (OVX + O + A), pantoprazole (OVX + P) and pantoprazole and alendronate (OVX + P + A). Omeprazole – Helicid 40 (Zentiva), pantoprazole – Controloc (Altana Pharma AG) and alendronate sodium, substance (Polpharma S.A.) were used in the study. Alendronate was administered in a dose of 3 mg/kg by a gastric tube (*p.o.*) in morning hours, whereas omeprazole or pantoprazole (3 mg/kg *i.p.*) in afternoon hours for 28 days. Upon discontinuation of drug administration, the animals were killed and the bones have been isolated: tibial (left and right) and femoral (left and right).

Bone tissue remodeling processes were characterized based on estimation of quantity and histomorphometric parameters of cancellous and compact bone. The effect of the drugs on the cancellous bone was estimated based on parameters describing bone formation and/or resorption (the width of bone trabeculae in the epiphysis and metaphysis of the femur), whereas the effect on the compact bone has was estimated based on parameters describing bone formation (transverse growth and the osteoid width in the tibial diaphysis, from the periosteum and endosteum side), as well as resorption (the tibial marrow cavity transverse cross-section surface and the marrow cavity surface/whole tibial diaphysis surface ratio). The cortical bone surface as well as whole tibial bone diaphysis surface were also examined.

Estimation of histomorphometric parameters was carried out on histological specimens prepared from sections of non-decalcified bones, obtained as a result of cutting right tibial diaphysis and distal right femoral epiphysis (24). In order to determine transverse growth of the tibial diaphysis, all rats were administered tetracycline hydrochloride twice (20 mg/kg *i.p.*, substance (Sigma)), 24 h before the start of the drug administration and 24 h before killing of the animals. The distance between the fluorescent stripes of tetracycline built to the new-formed bone was measured (25). Histomorphometric estimation of the specimens was carried out using a set including Optiphot-2 Nikon microscope with visible and ultraviolet light scope, a RGB video camera (Cohu), and a personal computer and Lucia G 4.51 software for digital histological measurements.

Quantity parameters determined in the present study included: bone mass per 100 g body mass and bone mineral substance mass (assayed by the mineralization method (26)) per 100 mg bone mass. The length and diameter of the tibia and femur were also measured.

The results are presented as the arithmetical means ± SEM. Statistical estimation was carried out

Table 1. Body mass gain and quantity parameters of the long bones after administration of omeprazole (3 mg/kg *i.p.*) or pantoprazole (3 mg/kg *i.p.*) and alendronate (3 mg/kg *p.o.*) for 28 days in ovariectomized rats.

Groups	Body mass gain after 28 days [g]	Bone mass [mg/100 g of body mass]		Bone mineral mass [mg/100 mg of bone mass]	
		Tibia	Femur	Tibia	Femur
NOVX	14.10 ± 1.35	200.18 ± 8.52	298.63 ± 5.27	48.72 ± 2.24	44.78 ± 0.37
OVX	42.00 ± 2.92 ***	189.59 ± 3.48	265.88 ± 3.61 ***	42.71 ± 0.39 **	42.01 ± 0.29 ***
OVX + A	43.38 ± 2.60	194.50 ± 1.82	270.64 ± 3.16	44.92 ± 0.54 oo	43.19 ± 0.48
OVX + O	44.00 ± 4.68	179.87 ± 5.44	261.93 ± 3.51	43.14 ± 0.99	40.59 ± 0.52 o
OVX + O +A	38.86 ± 1.90	191.11 ± 3.06	268.68 ± 4.11	44.89 ± 0.42 oo m	42.28 ± 0.47 m
OVX + P	45.38 ± 3.59	182.49 ± 1.91	258.14 ± 4.16	41.81 ± 0.78	40.31 ± 0.45 o
OVX + P +A	33.29 ± 4.70	198.02 ± 4.38 p	278.91 ± 7.66 pp	44.91 ± 0.53 oo pp	41.92 ± 0.44 a p

NOVX – non-ovariectomized control rats, OVX – ovariectomized control rats, OVX + A – ovariectomized rats receiving alendronate, OVX + O – ovariectomized rats receiving omeprazole, OVX + O + A – ovariectomized rats receiving omeprazole and alendronate, OVX+P – ovariectomized rats receiving pantoprazole, OVX + P + A – ovariectomized rats receiving pantoprazole and alendronate. Results are presented as the means ± SEM (n = 8–10). * – Significantly different from the NOVX control rats: ** $p < 0.01$, *** $p < 0.001$. o Significantly different from the OVX control rats: o $p < 0.05$, oo $p < 0.01$. m Significantly different from the ovariectomized rats receiving omeprazole: $p < 0.05$. p Significantly different from the ovariectomized rats receving pantoprazole: p $p < 0.05$, pp $p < 0.01$. a Significantly different from the ovariectomized rats receving alendronate: $p < 0.05$.

based on the analysis of variance (using Statistica 7 computer program). After confirmation of statistically significant differences in ANOVA ($p < 0.05$), further analysis was carried out by means of Duncan's *post-hoc* test. In case of the lack of homogeneity of variance (Levene's test), non-parametric tests were used: Kruskal-Wallis ANOVA and Mann-Whitney U test.

Differences between the groups: NOVX and OVX; OVX and OVX + A, OVX + O, OVX + O + A, OVX + P, OVX + P + A, as well as differences between the groups: OVX + O + A and OVX + O or OVX + A, and OVX + P + A and OVX + P or OVX + A were estimated. The differences were regarded as statistically significant with $p < 0.05$.

RESULTS

Body mass gain and the long bones quantity parameters after the administration of omeprazole or pantoprazole and alendronate in rats

Estrogen deficiency in OVX control rats caused statistically significant, comparing to the NOVX control group, 187.7% increase of body mass gain, 11.0% decrease of femoral mass/100 g body mass, 12.3% decrease of the tibial mineral substance mass/100 mg bone mass and 6.2% decrease of femoral mineral substance mass/100 mg bone mass (Table 1). After administration of omeprazole and pantoprazole, mineral substance mass/100 mg bone mass in the femur decreased significantly by 3.4 and 4.1%, respectively, in comparison with the OVX group. Alendronate significantly increased tibial mineral substance mass/100 mg bone mass by 5.2% (Table 1). Omeprazole and pantoprazole did not change the effect of alendronate on mineral substance mass in the tibia. However, they caused a decrease of mineral substance mass /100 mg bone mass in the femur comparing to the results in rats receiving alendronate: omeprazole insignificantly by 2.16%, and pantoprazole significantly by 3.16% (Table 1). There were no significant changes of in the bone length and diameter after administration of omeprazole or pantoprazole in ovariectomized rats (data not shown).

Histomorphometric parameters of the tibia after the administration of omeprazole or pantoprazole and alendronate

Estrogen deficiency induced by bilateral ovariectomy caused a statistically significant decrease of tibial cortical bone surface and the whole tibial diaphysis surface, comparing to the NOVX control group, by 8.2% and 7.1%, respectively, and a statistically insignificant increase (by 5.0%) of the ratio of marrow cavity surface to whole diaphysis surface. Alendronate did not significantly change the effect of estrogen deficiency on those parameters. However, omeprazole and pantoprazole increased the effect of estrogen deficiency on the cortical bone surface, causing its statistically insignificant decrease comparing to OVX control group, by 3.9% and 3.4%, respectively (Table 2).

Table 2. Histomorphometric parameters of the tibia after administration of omeprazole (3 mg/kg *i.p.*) or pantoprazole (3 mg/kg *i.p.*) and alendronate (3 mg/kg *p.o.*) for 28 days in ovariectomized rats.

Groups	Transverse cross- section surface [mm^2]			Transverse cross-section marrow cavity/ diaphysis surface ratio	Transverse growth [µm]	
	marrow cavity	cortical bone	whole diaphysis		periosteal	endosteal
NOVX	0.869 ± 0.032	3.196 ± 0.103	4.065 ± 0.127	0.214 ± 0.005	38.28 ± 1.28	19.50 ± 0.69
OVX	0.849 ± 0.032	2.930 ± 0.053 *	3.778 ± 0.055*	0.225± 0.008	35.34 ± 1.37	19.82 ± 1.37
OVX + A	0.801 ± 0.046	2.906 ± 0.046	3.707 ± 0.062	0.216 ± 0.010	37.39 ± 0.67	21.29 ± 0.81
OVX + O	0.793 ± 0.049	2.817 ± 0.040	3.610 ± 0.073	0.219 ± 0.011	35.53 ± 1.33	19.04 ± 2.13
OVX + O + A	0.830 ± 0.024	2.827 ± 0.084	3.656 ± 0.083	0.228 ± 0.008	36.36 ± 1.77	20.18 ± 0.75
OVX + P	0.911 ± 0.064	2.828 ± 0.058	3.739 ± 0.094	0.242 ± 0.013	36.62 ± 1.13	19.03 ± 1.80
OVX + P + A	0.919 ± 0.034	2.899 ± 0.093	3.818 ± 0.113	0.241 ± 0.006 [a]	36.88 ± 0.64	17.17 ± 0.55 [a]

Group designations – see Table 1. Results are presented as the means ± SEM (n = 8–10). * Significantly different from the NOVX control rats: $p < 0.05$. [a] Significantly different from the ovariectomized rats receiving alendronate: $p < 0.05$.

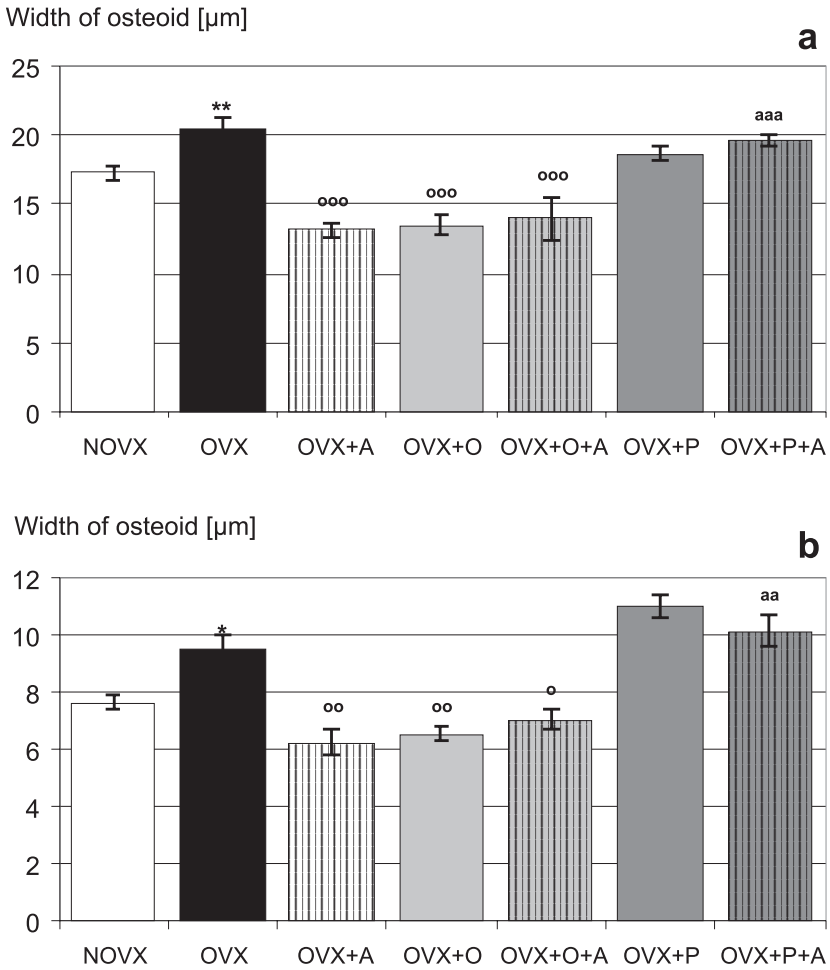

Figure 1. Width of periosteal (**a**) and endosteal (**b**) osteoid in the tibial diaphysis after administration of omeprazole (3 mg/kg *i.p.*) or pantoprazole (3 mg/kg *i.p.*) and alendronate (3 mg/kg *p.o.*) for 28 days in ovariectomized rats. Group designations – see Table 1. Results are presented as the means ± SEM (n = 8–10). * Significantly different from the NOVX control rats: * $p < 0.05$, ** $p < 0.01$. ° Significantly different from the OVX control rats: ° $p < 0.05$, °° $p < 0.01$, °°° $p < 0.001$. [a] Significantly different from the ovariectomized rats receiving alendronate: [aa] $p < 0.01$, [aaa] $p < 0.001$

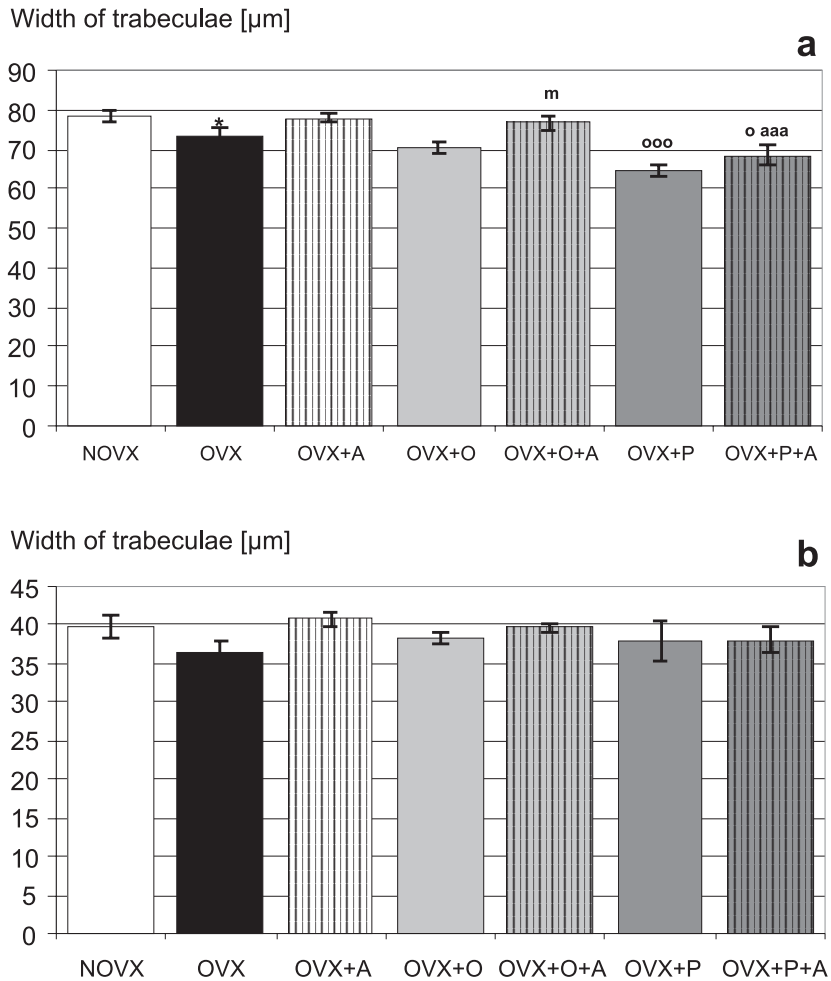

Figure 2. Width of trabeculae in the distal epiphysis (**a**) and metaphysis (**b**) of the femur after administration of omeprazole (3 mg/kg *i.p.*) or pantoprazole (3 mg/kg *i.p.*) and alendronate (3 mg/kg *p.o.*) for 28 days in ovariectomized rats. Group designations – see Table 1. Results are presented as the means ± SEM (n = 8–10). * Significantly different from the NOVX control rats: $p < 0.05$. ^{o} Significantly different from the OVX control rats: ^{o} $p < 0.05$, ^{ooo} $p < 0.001$. ^{m} Significantly different from the ovariectomized rats receiving omeprazole: $p < 0.05$. ^{a} – Significantly different from the ovariectomized rats receiving alendronate: ^{aaa} $p < 0.001$

Omeprazole did not change the effect of alendronate on the cortical bone surface, marrow cavity surface and whole diaphysis surface as well as the marrow cavity surface to the whole diaphysis surface ratio. On the contrary, pantoprazole used along with alendronate impaired the alendronate effect. In comparison with the group receiving alendronate, it significantly increased the marrow cavity surface to the whole diaphysis surface ratio by 11.7% and, statistically insignificantly (by 14.7%), the surface of the marrow cavity (Table 2).

Estrogen deficiency in ovariectomized control rats significantly increased the osteoid width from the periosteum side (by 17.8%) and from the marrow cavity side (by 23.9%) in comparison with the NOVX control group (Figs. 1a and 1b). Alendronate, comparing to the OVX control group, significantly decreased the osteoid width from the periosteum and marrow cavity side by 35.5% and 33.9%, respectively. Omeprazole, comparing to the OVX control group, significantly decreased the osteoid width from the periosteum side by 33.8% and from and the marrow cavity side by 30.8%, and administered along with alendronate by 31.4% and 25.7%, respectively (Figs. 1a and 1b). Pantoprazole, administered along with alendronate, comparing to the group receiving alendronate, caused a statistically significant increase of the osteoid width from the periosteum side by 49.5% and from the marrow cavity side by 62.0% (Figs. 1a and 1b), as well as a significant decrease (by 19.4%) of the tibial diaphysis growth from the marrow cavity side (Table 2).

Histomorphometric parameters of the femur after the administration of omeprazole or pantoprazole and alendronate

Estrogen deficiency in the OVX control rats decreased the width of bone trabeculae in the femoral epiphysis by 6.2% in comparison with the NOVX control rats (Fig. 2a). Alendroniane decreased the effect of estrogen deficiency, causing an increase of the width of bone trabeculae in the epiphysis by 5.9% and in the metaphysis by 11.4% (Fig. 2b). Omeprazole did not significantly change the effect of estrogen deficiency on the width of bone trabeculae, however, pantoprazole caused a statistically significant, comparing to the OVX control group, decrease of the width of bone trabeculae in the femoral epiphysis by 12.3% (Fig. 2a). Omeprazole administered along with alendronate did not significantly change the effect of alendronate on the width of bone trabeculae in the femoral epiphysis and metaphysis (Figs. 2a and 2b). On the contrary, pantoprazole administered along with alendronate significantly decreased the width of bone trabeculae in the femoral epiphysis by 6.8% comparing to the OVX control group and by 12.0% comparing to the results in rats receiving alendronate (Fig. 2a).

DISCUSSION

Estrogen deficiency in bilaterally ovariectomized rats caused disorders of bone remodeling indicating the increase of resorption processes as well as inhibition of bone formation and mineralization processes. Intensification of resorption in trabecular bone caused a decrease of width of trabeculae in the distal femoral epiphysis and, in compact bone, an increase of the tibial marrow cavity surface/whole diaphysis surface ratio. A decrease of the diaphysis cortical bone surface and a decrease of the periosteal transverse growth are arguments for inhibition of bone formation. An increase of the width of periosteal and endosteal osteoid in the tibia is an argument for mineralization process inhibition.

Changes in quantity parameters (a decrease in the mineral substance mass/bone mass ratio in the tibia and femur, a decrease in the femoral mass/body mass ratio) may indicate intensification of bone resorption and/or insufficient bone formation and mineralization response in ovariectomized rats. A significant increase of body mass gain was also a consequence of estrogen deficiency in ovariectomized rats. The changes in trabecular and compact bone structure, which are the evidence of intensification of bone loss, indicate development of osteopenia in bilaterally ovariectomized rats and are consistent with results of other authors' studies (1–3, 5, 6).

Omeprazole or pantoprazole were administered to bilaterally ovariectomized rats in the 3 mg/kg mc. (*i.p.*) dose. This dose was chosen based on most often used 24-h doses in patients (20–40 mg), considering commonly used ten-fold conversion rate resulting from faster metabolism in rats.

Results of the histomorphometric study showed that pantoprazole impaired bone remodeling in rats with estrogen deficiency more than omeprazole. Pantoprazole intensified bone resorption and inhibited bone formation in trabecular and compact structure of bone. In trabecular bone it caused a decrease of the width of bone trabeculae in the femoral epiphysis, yet in compact bone – an increase of the marrow cavity surface and the marrow cavity surface/whole diaphysis surface ratio in the tibia. Pantoprazole also impaired the mineralization process, indication of which may be the increase of the osteoid width from the marrow cavity side. Slighter changes in bone remodeling, with the exception of bone formation process inhibition (a decrease of the osteoid width in the tibia), were also observed after administration of omeprazole. A significant decrease of the mineral substance mass/bone mass ratio in the femur as well as a decrease of the femoral bone mass/100 g body mass ratio were a reflection of impaired bone remodeling processes after administration of omeprazole or pantoprazole in rats with estrogen deficiency. The latter observation is consistent with the results of Cui et al. (19), who observed the decreased bone mineralization in young rats. However, recent *in vitro* study on the effect of omeprazole on the expression of transcription factors in osteoclasts and osteoblasts demonstrated that the drug decreased the activation of osteoclasts and increased that of osteoblasts (27), which is inconsistent with our results.

The histomorphometric and quantity (the mineral substance mass/bone mass ratio) changes after use of the proton pump inhibitors demonstrated in the present study, indicate the intensification of resorption processes leading to bone mass loss in rats with estrogen deficiency. Impairment of bone mineralization process observed after pantoprazole may be the result of the increase of remodeling rate and insufficient bone formation in response to the increased bone resorption.

Adverse changes in bone turnover in rats with estrogen deficiency show that inhibitors of the proton pump (H^+/K^+-ATPase), which is present in the stomach, in the dose of 3 mg/kg *i.p.* do not inhibit

the vacuolar proton pump (V-ATPase) in ruffled border of osteoclasts, since they did not exert the protective action on the bones. The results obtained in the *in vivo* study showing that the examined H^+/K^+-ATPase inhibitors not only did not inhibit the resorption, but additionally increased it, remain in contradiction with previous *in vitro* studies (28, 29) as well as a clinical study indicating a decrease of resorption in adult patients after administration of omeprazole (21). However, based on literature data regarding degradation and activation of omeprazole, it can not be ruled out that proton pump inhibitors (H^+/K^+-ATPase) do not undergo conversion into active metabolites in the osteoclast resorption cavity environment where pH is 4.5–6.0 (4, 30). Omeprazole or pantoprazole protonation into active metabolites in the tubules of stomach parietal cells occurs in pH approx. 1.0 (12). The lack of inhibitory effect of omeprazole and pantoprazole on bone resorption in the present study may be explained by the possible lack of their conversion into active metabolites in the resorption cavity environment.

The results on the adverse effect of omeprazole and pantoprazole on bone tissue obtained in the present study are consistent with recent clinical observations, which indicate that proton pump inhibitor therapy increases the risk of hip fracture (22) or other fracture (31). Wright and Proctor (32) suggest that the increase of hip fracture after the use of proton pump inhibitors may be the effect of decreased intestinal absorption of calcium and increased bone mass loss. Alike, Kirkpantur and Altun (33) showed a decrease of bone mineral density in hemodialyzed patients who were administered omeprazole. The results of the present study show that prolonged pantoprazole or omeprazole therapy may increase the risk of osteoporosis development, especially if the drugs are administered to estrogen deficient women.

Also the effect of omeprazole or pantoprazole administered concurrently with alendronate on bone remodeling processes in rats with estrogen deficiency was studied in this work. Histomorphometric study showed that proton pump (H^+/K^+-ATPase) inhibitors, especially pantoprazole, impair the antiresorptive effect of alendronate, both in compact and trabecular bone. In compact bone of the tibia, comparing to rats receiving alendronate alone, a significant increase of the marrow cavity surface/whole diaphysis surface ratio was observed, whereas in trabecular bone of the femur – a significant decrease of the width of bone trabeculae in the epiphysis was demonstrated. Pantoprazole also inhibited bone formation (decreasing the endosteal transverse growth) and impaired bone mineralization (increasing the osteoid width and decreasing the ratio of bone mineral substance mass to bone mass in the femur).

Based on the results of the present study it may be concluded that proton pump (H^+/K^+-ATPase) inhibitors, especially pantoprazole, administered along with alendronate, impair its preventive effect on the development of osteopenia caused by estrogen deficiency in bilaterally ovariectomized rats. Prolonged use of proton pump (H^+/K^+-ATPase) inhibitors in prevention or therapy of inflammatory states of esophagus and gastric ulcer disease caused by alendronate may impair its anti-osteoporotic effect.

CONCLUSIONS

Pantoprazole intensified osteoporotic changes caused by estrogen deficiency in ovariectomized rats more than omeprazole. Bone remodeling disorders were the consequence of the intensification of bone resorption with concurrent inhibition of bone formation and mineralization.

Pantoprazole and, to lesser extent, omeprazole weakened the preventive effect of alendronate on bone remodeling in ovariectomized rats.

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