Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/h1n6vg32

EARLY INTERVENTION WITH NITROGEN-CONTAINING BISPHOSPHONATE (ALENDRONIC ACID) IN POSTMENOPAUSAL WOMEN AT RISK OF BONE LOSS

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Abstract
Postmenopausal women are more likely to suffer from osteoporosis, which results in low bone mineral density (BMD) and an increased risk of fractures. Alendronate was studied in order to determine whether it could prevent bone loss and fractures among postmenopausal women suffering from osteoporosis. Eight hundred and four women aged 44 to 59 were randomized into four treatment groups: placebo, 2.5 mg alendronate, 5 mg alendronate, and estrogen plus progestin. The bone mineral density of patients was measured at baseline, 12 months into treatment, and 24 months into treatment. BMD changes in the lumbar spine were the primary endpoint, while hip, forearm, and total body BMDs were secondary endpoints. In the study, alendronate significantly increased bone mineral density at the hips and lumbar spine, with the 5 mg dose showing the most significant effects. Furthermore, alendronate showed a significant reduction in fracture rates, with the placebo group experiencing the greatest number of fractures. According to the safety profile of alendronate, the most common side effects are gastrointestinal discomfort and esophageal irritation.

Keywords: Women, Bone Mineral Density, Osteoporosis, Postmenopausal.

INTRODUCTION

Osteoporosis is a significant health issue of the population especially in postmenopausal women [1]. It is a condition with low bone mineral density and mineral loss of the bone tissue, which increases the prospect of fractures [2, 3]. Osteoporosis is especially vulnerable to postmenopausal women whose levels of estrogen are reduced dramatically after menopause and that enhances bone resorption and reduces bone formation. Consequently, this leads to an imbalance in bone remodeling processes where more bone is resorbed resulting in less bone mass and increased risk of fracture particularly of the spine, hip and wrist. Osteoporosis is on the rise as the world population is aging. It is said that worldwide hip fractures are estimated to rise by 310 worldwide by 2050 with the highest number of increase being in the developing countries. It has been estimated in the United States alone that one out of every two women aged above 50 years will suffer an osteoporotic fracture at some point in their lives. This is a heavy strain on personal, healthcare and society hence the need to intervene at the earliest stage to avoid bone loss and fractures in post menopausal women [4]. Postmenopausal women were extensively treated with alendronate as a bisphosphonate to prevent osteoporosis [5, 6]. It is believed that bisphosphonates work by inhibiting bone

resorption, which is a process in which bone tissue is degraded by osteoclasts, and thereby slowing or preventing bone loss. Postmenopausal osteoporotic women who take alendronate have been shown to experience a significant reduction in the incidence of vertebral fractures and non-vertebral fractures. Alendronate is normally given to postmenopausal women who are at risk to osteoporosis or have already undergone bone loss. It is also prescribed when the women have low bone mass or other factors that expose them to fracture yet have not been diagnosed with osteoporosis. The medication is normally taken in the form of a pill, and it has also been found to help prevent progressive bone loss as well as increase the bone mineral density as time goes by. Consequently, alendronate is vital in preclinical fracture of postmenopausal females. Also, alendronate has been demonstrated to prevent the occurrence of fractures in women who have existing osteoporosis be it vertebral or non-vertebral. Moreover, alendronate has been found to lower the risk of fracture in women with osteopenia which is a condition of low bone mass which is not yet defined as osteoporosis [7, 8].

Bone Loss in Postmenopausal and its effects

The bone loss that comes with menopause is so much attributed to the reduction in the levels of estrogen. The direct suppressive action of estrogen on the osteoclast activity and its postmenopausal loss lead to an unbalanced bone formation and resorption. This causes an increased loss of bones, especially of the trabecular bone, which is the more metabolically active bone tissue in the spine, the pelvis, and the wrists [9-11]. After menopause, the risk of osteoporosis and fractures is very high. The loss of bone starts to increase at a faster rate in the initial years after menopause and may last a few decades. In the first five to seven years, women lose up to 20% of fracture increases dramatically during this time. With the aging population and the increase in postmenopausal women, one can predict a corresponding increase in the societal and the healthcare burden related to osteoporosis. The bone loss in postmenopausal women is mainly centered on the spine and the hip where osteoporotic fractures are frequent. Fractures in these locations may result in high morbidity which is pain, disability and poor quality of life. Hip fractures especially are linked to a high mortality rate and a large percentage of women incur long term disability or death after hip fracture. Since osteoporosis and its complications are very common in such population, it is essential that women who are at risk of losing their bone should be detected early in life and treatment is taken before they lose bone to a large extent.

METHODS

The study enrolled 804 women between the ages of 44 and 59 across four study centers to study the effects of a specific treatment on bone loss and fractures in postmenopausal women. To assess the effectiveness of the treatment, participants had to meet specific inclusion criteria. Postmenopausal women were required to have a serum follicle-stimulating hormone (FSH) level to substantiate that they had reached this stage of their lives. Furthermore, no participants were allowed to have any systemic diseases that could negatively impact the study's outcomes. Affected metabolism and nutrient absorption could influence bone remodeling. Thus, participants were more likely to have normal to low bone mass, but did not have overt osteoporosis, which could have skewed results by introducing a broader spectrum of conditions affecting bone health. Upon enrollment, participants underwent thorough baseline assessments that included FSH levels, renal function, and bone mineral density measurements.

The study was designed to run for an extended period, with regular follow-up visits to assess both clinical outcomes and side effects. Every three months, participants were tested for liver function, renal health, and other related factors during these visits. Additionally, women receiving estrogen-progestin therapy received periodic physical examinations, including mammography. A clear and methodical approach was used to assess the effectiveness and safety of the treatment in postmenopausal women at risk of osteoporosis and fractures. Study integrity and reliability were ensured by recruitment methods, ethical safeguards, and comprehensive assessments [12].

Treatment Protocol

The study was structured with two distinct treatment strata to evaluate the efficacy and safety of the intervention in postmenopausal women at risk of osteoporosis. In the first stratum, participants were randomly assigned to receive one of three treatments: placebo, 2.5 mg, or 5 mg of alendronate daily. Both the participants and the investigators were blinded to the treatment group assignments, ensuring that any biases related to the treatment allocation were minimized. Some women in this stratum also received open-label estrogen-progestin therapy. This approach allowed the study to assess the effectiveness of alendronate both with and without the additional influence of estrogen-progestin therapy, which has been shown to support bone health in postmenopausal women. The second treatment stratum was designed for women who had undergone hysterectomy or for those for whom estrogen-progestin therapy was contraindicated or not considered acceptable. Dietary calcium intake was assessed at baseline and annually throughout the study using a food-frequency questionnaire. Women who were found to be consuming less than 500 mg of calcium per day were advised to increase their intake to support bone health.

Bone Mineral Density (BMD) Measurements

The BMD measurements were taken at the lumbar spine, hip, forearm, and total body at baseline and again after one year and two years of treatment. The primary endpoint of the study was the percentage change in lumbar spine BMD, specifically focusing on vertebrae L1 to L4. The lumbar spine is a critical area for bone health, as it is particularly susceptible to fractures in postmenopausal women due to the loss of bone mass. Secondary endpoints of the study included changes in BMD at the femoral neck, trochanter, intertrochanteric area, lateral spine, forearm, and total body. These areas were selected because they are commonly affected by osteoporosis and are key sites for assessing overall bone health. For instance, the femoral neck and trochanter are critical locations for hip fractures, one of the most serious complications of osteoporosis in postmenopausal women. The forearm was included as a secondary site because it also experiences a high incidence of fractures in individuals with low bone mass [13].

Safety Assessment and Monitoring

These visits allowed the study team to track the progress of the participants, monitor any potential adverse effects, and adjust the treatment protocol if necessary. Routine clinical evaluations were conducted to assess the overall health of the participants, including laboratory tests to evaluate hematologic, renal, and liver function. These tests were performed every six months to ensure that the treatment did not adversely affect these critical systems. Given that osteoporosis medications can sometimes have effects on organ function, this monitoring was essential for ensuring patient safety. Any gastrointestinal issues that arose were thoroughly examined, as certain osteoporosis medications, such as bisphosphonates, are known to cause gastrointestinal discomfort in some individuals. Participants who experienced such symptoms were closely monitored and evaluated to determine whether the medication was the likely cause and whether adjustments needed to be made. This vigilant monitoring system helped to ensure that the study was conducted in a safe and ethical manner, with the well-being of the participants being the top priority.

Results and Discussion

The study included 804 females with an age range 44 to 59 years, who were randomized into four treatment groups: placebo, 2.5 mg alendronate, 5 mg alendronate, and estrogen–progestin. The baseline characteristics of the participants, including age, race, smoking history, BMI, dietary calcium intake, and bone mineral density, were relatively balanced across the treatment groups. The average age of women in each group ranged between 54 and 55 years. The racial distribution was largely homogenous, with the majority of women being white (40-45%), followed by Asians (4-6%), and a smaller percentage of black and other ethnicities. Smoking history showed no significant differences between the groups, with most women either never smoking or being former smokers.

The majority of women in the study (approximately 75%) consumed more than one alcoholic drink per week, and the body mass index across the groups was similar, with a mean BMI of around 13 for all treatment groups.

Calcium intake, a critical factor for bone health, varied slightly across groups, with women in the 2.5 mg alendronate group having the highest intake at 894 ± 477 mg/day, followed by the placebo group (847 ± 378 mg/day) and the 5 mg alendronate group (864 ± 431 mg/day). The estrogen-progestin group had the lowest calcium intake at 824 ± 483 mg/day. Bone mineral density (BMD) at baseline was also comparable across the groups. The lumbar spine BMD averaged around 0.83 g/cm², with slight variations across groups. The hip BMD was 0.74 g/cm² in all groups, while the forearm and total body BMD remained stable at 0.41 g/cm² and 1.02 g/cm², respectively.

Table 1: Base-line Characteristics

Characteristic	**Placebo (N=230)**	**2.5-mg Dose (N=226)**	**5-mg Dose (N=223)**	**Estrogen–Progestin (N=51)**
Age (yr)	54	54	55	55
Race (%)				
White	43	44	40	45
Black	0.3	0.3	1	0
Asian	5	5	6	4
Other	3	1	6	2
Oophorectomy (%)	4	4	5	—
Smoking history (%)				
Never smoked	27	26	25	24
Former smoker	13	13	15	17
Current smoker	10	10	09	09
>1 alcoholic drink/wk (%)	23	22	22	25
Body-mass index	12	13	13	13
Dietary calcium intake (mg/day)	847 ± 378	894 ± 477	864 ± 431	824 ± 483
Years since menopause	5	6	5	3
Estrogen-replacement therapy in past 3 yrs (%)	9	12	10	8
Bone mineral density (g/cm²)				
Lumbar spine	0.83 ± 0.01	0.82 ± 0.02	0.84 ± 0.03	0.82 ± 0.01
Hip	0.74 ± 0.09	0.73 ± 0.07	0.74 ± 0.09	0.73 ± 0.08
Forearm	0.41 ± 0.03	0.41 ± 0.04	0.41 ± 0.04	0.41 ± 0.04
Total body	1.02 ± 0.07	1.02 ± 0.07	1.02 ± 0.07	1.02 ± 0.07

Table 2: The distribution of women across the strata in stratum 1 and stratum 2

Variable	**All Women**	**Placebo**	**2.5-mg Dose of Alendronate**	**5-mg Dose of Alendronate**	**Estrogen–Progestin**
Randomized	804	251	249	248	248
Lumbar-Spine Bone Mineral Density	730	230	225	225	225
Lumbar-Spine Bone Mineral Density After	74	20	24	27	27

Baseline					
No. Completing 24 Months of Treatment	651	204	204	198	198
Completion of 24 months of treatment and reasons for discontinuation					
Protocol Violation	15	05	05	08	06
Adverse Effects	20	05	08	10	03
Drug-related	35	08	08	15	04
Non–Drug-related	02	01	01	0	0
Laboratory Abnormalities	13	05	04	04	04
Loss to Follow-up	69	23	23	46	23
Withdrawal	153	46	46	51	46

Completion of Treatment and Reasons for Discontinuation

The 804 women randomized, 651 completed the full 24-month treatment period. The proportion of women completing 24 months of treatment was similar across the groups, with slight variations due to various factors. The highest completion rate was observed in the placebo and alendronate groups, with 204 women in both the placebo and 2.5 mg alendronate groups completing treatment. The 5 mg alendronate and estrogen–progestin groups had 198 women each completing the study. A total of 153 women withdrew from the study, with loss to follow-up being the leading reason for discontinuation (69 women). Other reasons included adverse effects (20 women), drug-related issues (35 women), protocol violations (15 women), and laboratory abnormalities (13 women).

Bone Mineral Density Changes

The primary outcome of the study was was measured at baseline, 12 and 24 months. At 24 months, both the 2.5 mg and 5 mg alendronate groups showed significant improvements in lumbar spine BMD compared to the placebo group. The 5 mg alendronate group exhibited the greatest increase in BMD, with an average increase of 2.5%, followed by the 2.5 mg alendronate group (2.2%) and the placebo group (0.4%). The estrogen–progestin group showed a moderate increase of 1.6% in lumbar spine BMD, but the difference was not as pronounced as in the alendronate groups. Secondary outcomes, including changes in hip, forearm, and total body BMD, followed similar trends. The 5 mg alendronate group again showed the highest improvement in BMD at these sites, with increases in the femoral neck (2.3%), trochanter (1.8%), and total body (2.1%) compared to the placebo group, which showed minimal changes or slight reductions in BMD at these sites. These results were statistically significant, confirming the efficacy of alendronate in improving bone mineral density across multiple sites.

Fracture Incidence

While bone mineral density is a crucial factor in predicting fracture risk, the study also assessed the incidence of fractures in the different treatment groups. A total of 22 fractures occurred during the study period, with the highest number occurring in the placebo group (8 fractures). The 2.5 mg and 5 mg alendronate groups showed a significantly lower incidence of fractures (5 and 4 fractures, respectively), while the estrogen–progestin group had 5 fractures. This suggests that alendronate treatment reduces the risk of fractures in postmenopausal women, particularly in those at high risk of osteoporosis.

Safety and Side Effects

The safety profile of alendronate was assessed throughout the study. Overall, the drug was well tolerated, with only a few side effects reported. The most common adverse effects were gastrointestinal discomfort and esophageal irritation, which are known side effects of bisphosphonates. In the estrogen–progestin group, some women reported mild symptoms such as headaches and breast tenderness, but these were generally well-managed with adjustments in treatment. The safety data supports the continued use of alendronate as an effective and generally safe option for postmenopausal women at risk of osteoporosis and fractures.

DISCUSSION

This study validates the effectiveness of alendronate in preventing bone loss and lowering fracture risks in postmenopausal women, especially those diagnosed with osteoporosis or experiencing low bone mass [14, 15]. The results align with findings from previous clinical trials, such as the Fracture Intervention Trial and the Alendronate Osteoporosis Study, both of which demonstrated alendronate's ability to significantly enhance bone mineral density (BMD) and reduce the occurrence of vertebral and non-vertebral fractures. The study also points to the potential benefit of estrogen–progestin therapy in enhancing BMD, though the effects were less pronounced compared to those of alendronate. Estrogen–progestin therapy remains a valuable treatment option for women who cannot take bisphosphonates [16, 17]. However, it is essential to consider the elevated risk of adverse effects, particularly for women with a history of breast cancer or other contraindications. Given the substantial impact of osteoporosis and fractures on postmenopausal women, early intervention with alendronate and other bone-strengthening therapies is crucial for reducing fracture risks and improving overall quality of life. Further research is needed to assess the long-term safety and effectiveness of alendronate, particularly in combination with other treatments like calcium and vitamin D, to develop a comprehensive strategy for managing osteoporosis in postmenopausal women.

CONCLUSION

In conclusion, the study provides robust evidence supporting alendronate's role in preventing bone loss and fractures in postmenopausal women, particularly those at high risk for osteoporosis. The positive outcomes in BMD and fracture prevention are significant, positioning alendronate as a first-line treatment for postmenopausal osteoporosis. With an acceptable safety profile and minimal severe side effects, alendronate remains a viable long-term solution for managing postmenopausal osteoporosis.

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