Effect of a Short-Term Treatment with Once-A-Week Medication of Alendronate 70 Mg on Bone Turnover Markers in Postmenopausal Women with Osteoporosis

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Objective: *The study was carried out to evaluate safety and efficacy of once-a-week medication of Kasparalendronate for inhibiting high bone turnover rate.*

Material and Method: *Forty-nine postmenopausal osteoporotic participants were included in the study. This investigation was carried out as an open study. The participants received the drug every week for 12 weeks. Pain, drug side effects and bone turnover markers were evaluated at the 6th week and 12th week after the first visit.*

Results: *None had significant complication and all could complete the trial. Thirteen participants, (26.3%), had minimal side effects, which the trial drug could be administered until the end of study. At the 12th week follow-up, 42/49 participants (85.7%) had normal serum Beta-crosslab and 45/49 participants (91.8%) had normal serum N-MID osteocalcin. None showed any decrease in serum P1NP. All participants had slight reduction in serum alkaline phosphatase.*

Conclusion: *The trial drug could inhibit high bone turnover in about 85% of post-menopausal participants within 12 weeks of drug administration and no severe side effect took place.*

Keywords: *Bisphosphonates, Bone resorption, Osteoporosis*

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Alendronate is the most common drug to be used for the management of post-menopausal osteoporosis[1,2]. It is an effective drug for the prevention of primary and secondary osteoporotic fractures[3-5]. The main mechanism of the drug aims to slow down bone turnover rate by reducing osteoclast on bone resorption. The original drug, Fosamax®, has rapid onset on inhibiting bone resorption which results in normalizing serum Betacrosslab and serum N-MID osteocalcin in all participants within 12 weeks[6-8]. Recently, many new generic alendronates have become available in Thailand, which can reduce the cost of treatment. One of the generic drugs is the once-a-week application of Kaspar's oral alendronate 70 mg, which has an encouraging pharmacologic profile. Its disintegration time is similar to the original drug. The objective of the study was to find out the efficacy of this generic drug on bone turnover markers and its safety.

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Material and Method

For the sample size calculation, the program nQuery advisor was used and the number of the participants in this study was 35 and was estimated that 90% of them would have normal serum Betacrosslab after Kaspar alendronate administration within 12 weeks; the alpha error was 0.05.

The trial has been carried out at the Department of Orthopedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University. The inclusion criteria of the study were 1) participants who had post-menopausal osteoporosis with one, or more than one, clinically healed osteoporotic fracture, 2) participants who had T-scores of BMD at the spine and femoral neck below -2.5, 3) participants who had normal complete blood count tests, fasting blood sugar, renal and liver functions, 4) participants who had normal to high serum N-MID osteocalcin, high serum Beta-crosslab, >0.32 ng/ml and normal to high serum P1NP and 5) participants who had never received any bisphosphonates before the study. The exclusion criteria were 1) participants who had any significant upper gastrointestinal problems, 2) participants who could not be followed-up as per the schedule, 3)

participants who continued previous regular medication and laboratory tests, 4) participants who could not sit steady for at least half an hour after taking the drug, 5) participants who did not want to participate or continue with the study for any other reason at any time and 6) participants with a disease or medication which had an affect on bone metabolism. A volunteer, who was not a medical practitioner and was not one of the authors, introduced the trial to the participants at the clinic.

Blood tests for completed blood count, fasting blood sugar, uric acid, renal and liver function tests were carried out and all must be within normal limit. Bone turnover markers were measured by test kits of Roche Diagnostic Company. Bone turnover markers including 1) serum parathyroid hormone kit for the possibility of secondary osteoporosis (normal value, 15.00-65.00 pg/ml), 2) serum Beta-crosslab for evaluation of bone resorption (normal value, <0.32 ng/ml), 3) serum N-MID osteocalcin for evaluation of overall bone turnover rate (normal value, 1.00-35.00 ng/ml) and 4) serum P1NP for evaluation of new bone formation (normal value, 15.00-74.00 ng/ml), were used[9-11]. The serum vitamin D, 25OH calciferol, for all participants, must have been over 30 ng/ml before the trial.

The participants were informed about the trial and they had an agreement to participate in the study. All participants could discontinue the trial at anytime. This study was approved by the Siriraj IRB Ethics Committee, project number 239/2552 (ECI), 31/07/2552. All biographic data of the participants and pain characteristics were recorded in the Case Record Forms (CRFs) which had been approved by the Ethics committee. Pain severity was evaluated by the use of visual analog scale. Associated and underlying diseases of the participants were reviewed and recorded. All laboratory tests, plain radiographs and T-scores of BMD by dual energy x-ray absorptiometry using Ge LUNAR densitometer (Lunar Corporation, Madison, WI) of the participants were rechecked to confirm the diagnosis and recorded in the CRFs.

The once-a-week medication of Kaspar alendronate 70 mg was administered for the participants at the beginning of the study. They took the drug in the morning before breakfast with a glass of plain water, not mineral, and had to sit steady for at least half an hour after taking the drug before they performed any activities or had their breakfast. Oral multivitamin with 800 IU of vitamin D and 1,000 mg of calcium carbonate per day were administered to the participants continuously during the study. One capsule of 20,000 u vitamin D2 every 2 weeks was also administered for the participants to provide adequate vitamin D supplementation. Paracetamol and NSAIDs on demand were administered for the participants who still had musculoskeletal pain before the trial.

The participants were followed-up at the end of the 2^{nd}, 6^{th} and 12^{th} weeks after the first medication. Physical examinations with re-evaluation about pain and side-effects of the drug were carried out and the results were recorded. At the 6^{th} and 12^{th} week follow-up, blood tests for CBC, renal function, liver function and bone turnover markers were done. Particular participants, who still had severe pain (VAS >3) at the fractured site or related areas, had all physical findings re-evaluated by plain radiography as well as all indicated blood tests to discover any underlying conditions. The descriptive analysis was used for all data. Student-T test was used for analyzing the continuous data and Chi-square test and analysis of variance for analyzing the discrete data.

Results

Forty-nine post-menopausal osteoporotic participants with healed fractures underwent and completed the trial. Their ages ranged between 55 and 87 years old with an average of 71.48 ± 9.07 years old. All participants were female. Their BMI ranged between 17.1 and 35.88 with an average of 23.62 ± 4.01 kg/m^2. Thirty-seven participants, 75.5%, had associated osteoarthritis and most of them had their main problems at the knees, 33/37 (89.2%). Two participants had degenerative disease of the spine. The participants, who had healed osteoporotic fractures, accounted for spinal fractures in 20/49 (40.8%). All participants had clinical and radiological fracture healing before starting the trial. Deformities of the spine were found in 35 participants (71.4%), which showed kyphosis in 30 participants and scoliosis in 5 participants. Diabetes mellitus with good control was found in 10 participants (20.4%).

At the first visit, all the participants had significant pain with VAS above 3 (score = 5.23 ± 2.09) (Table 1). The enrolled participants had normal blood value of renal and liver functions test. All the participants had high bone turnover rate with Betacrosslap over 0.32 ng/ml (Table 2). Most of the participants had normal serum N-MID osteocalcin, P1NP and parathyroid hormone (Table 2).

At the 2^{nd} week follow-up, significant improvement in pain was found in all participants (VAS 0.55 ± 1.32) (Table 1). Six participants (12.24%)

experienced minimal side effects and one participants experienced more than one side effects including nausea in one participant, dyspepsia in one participant, muscle pain in one participant, constipation in one participant and edema in 4 participants (Table 1). However, all participants could continue the trial.

After the trial drug administration for 6 weeks, all participants still had minimal pain with VAS 0.41±1.17 (Table 1). All participants had normal range of blood value for blood sugar, renal and liver function test. Normal value of serum parathyroid hormone, N-MID osteocalcin and P1NP were found in most of the participants (Table 2). Normal value of serum Betacrosslab, <0.32 ng/ml, was found in 38/49 participants (77.6%) (Table 2). The percentage of reduction in bone marker for the bone suppression was shown in Table 3. Minimal side effects were found in six participants. Three participants had the side effects, which were found at the 2nd week follow-up. On the other hand, 3 participants who had their side effects at the 2nd week follow-up reported no side effects at the 6th week. Three more participants experienced minimal

Table 1. Changes of pain severity, renal and Liver function tests and gastrointestinal complications during the follow-up

Laboratory test (n = 49)	Before trial	At 2nd week	At 6th week	At 12th week	*p*-value
Visual analog scale	5.23±2.09	0.55±1.32	0.41±1.17	0.27±1.27	<0.001
Alkaline phosphatase	77.74±28.73	-	74.55±28.55	63.13±22.71	<0.001
Albumin	4.21±0.28	-	4.17±0.33	4.19±0.28	0.629
Globulin	3.08±0.59	-	3.21±0.37	3.20±0.38	0.183
BUN	15.03±6.11	-	14.64±5.77	15.19±5.52	0.675
Creatinine	0.83±0.18	-	0.82±0.18	0.87±0.22	0.054
Complications (n = 49)	-	6 (12.24%)	6 (12.24%)	5 (10.20%)	-
Nausea		1	-	-	
Vomiting		-	-	-	
Dyspepsia		1	1	1	
Muscle pain		1	3	3	
Edema		4	2	2	
Constipation		1	2	2	
Fever		-	1	-	
Other side effects		-	1	1	

The *p*-value by one-way repeated measures analysis of variance (ANOVA) followed by Bonferroni multiple comparisons at type I error of 0.05 levels. One patient might experience more than one side effect.

Table 2. Changes of bone turnover markers during the trial

	Before trial (%)	At 6th week (%)	At 12th week (%)
Beta-cross laps (n = 49)			
<0.32 ng/dl (normal)	0	38 (77.6)	42 (85.7)
≥0.32 ng/dl	49 (100)	11 (22.4)	7 (14.3)
N-MID osteocalcin (n = 49)			
1.00-35.00 ng/ml (normal)	37 (75.5)	41 (83.7)	45 (91.8)
>35.0 ng/ml	12 (24.5)	8 (16.3)	4 (8.2)
P1NP (n = 49)			
<15.00 ng/ml	2 (4.1)	0	0
15.00-74.00 ng/ml (normal)	31 (63.3)	43 (87.8)	46 (93.9)
>74.00 ng/ml	16 (32.7)	6 (12.2)	3 (6.1)
Parathyroid hormone (n = 49)			
<15 pg/ml	1 (2.1)	0	0
15.00-65.00 pg/ml (normal)	32 (68.1)	24 (51.1)	23 (46.9)
>65 pg/ml	14 (29.8)	23 (48.9)	26 (53.1)

Table 3. Average value and percent changing of bone marker

	Average at 0 week	Average at 6 weeks	% change	Average at 12 weeks	% change
P1NP	71.74	47.30	-34.05	29.67	-58.64
B-cross	0.58	0.23	-60.42	0.18	-68.34
PTH	59.71	73.82	+23.62	70.61	+18.24
N-MID	30.48	26.77	-12.18	20.91	-31.39
Vit-D	26.72	26.09	-2.36	26.49	-0.88
Alkaline	77.74	74.38	-4.31	63.63	-18.15

side effects at the 6th week follow-up (Table 2). There were constipation in 2 participants, muscle pain in 3 participants, fever in 1 participant, dyspepsia in 1 participant, edema in 2 participants and abnormal sensation in the lower limb in 1 participant. Three participants experienced more than one side effect. However, the side effects were minimal; all participants could continue the trial.

At the 12th week follow-up. The participants had minimal pain with VAS <3 with an average of 0.27±1.27 (Table 1). All participants had normal blood test values. Minimal side effects were observed in 5 participants (10.20%). Four participants already experienced those side effects at the previous follow-up and one more participants reported minimal side effects at 12th week (Table 1). The observed side effects were muscle pain in 3 participants, dyspepsia in 1 participant, edema in 2 participants, constipation in 2 participants and abnormal feeling in their lower limbs in 1 participant. In summary, there were 10/49 participants or 20.4%, who had minimal side effects during the trial. Serum parathyroid hormone value was normal in 23/49 participants (46.9%), and high in 26/49 participants (53.1%) (Table 2). For the bone turnover markers, serum Betacrosslab <0.32 ng/ml was found in 42/49 participants (85.7%). Still the 7/49 participants (14.3%) had serum Betacrosslab >0.32 ng/ml (Table 2). Forty-five participants (91.8%) had normal value of N-MID osteocalcin with an average of 20.92±10.80 ng/ml (Table 1 and 2). Forty-six participants (93.9%) had normal value of serum P1NP and 3/49 participants (6.1%) still had high value of serum P1NP (Table 2). The percentage of reduction in bone marker for the bone suppression is shown in Table 3.

Discussion

From the data, taking Kaspar once-a-week alendronate 70 mg could normalize serum Betacrosslab in 85.3% of the participants for the 12-week trial. This finding confirmed the efficacy of the drug for inhibiting bone resorption even though it was slightly lower than the expectation, which was 90% from the sample size calculation. The trial drug has slightly less effectiveness than the original drug, which can normalize bone resorption marker, the Beta-cross, within 12 weeks in all participants[6,8]. The efficacy of the drug was also demonstrated by the reduction of Beta-cross lab down 68.3% (Table 3) by comparing to the baseline value. Serum alkaline phosphatase significantly decreased during the 12th week follow-up, which might confirm the efficacy in slowing down bone turnover rate of the drug. However, more specific of alkaline phosphatase, which is bone alkaline phosphatase, should be used in further study. Furthermore, about 90% of the participants had normal serum N-MID osteocalcin, which reflected normal overall bone turnover at the 12th week. However, the serum parathyroid hormone of most participants increased at the 6th and 12thweek follow-up which might be the response of the body to the changes of serum calcium from the trial drug (Table 2). Interestingly, none had low P1NP at the 12th week follow-up, which revealed normal bone formation process. The process might not be over suppressed by the trial drug as it was usually found to be the case after the use of most bisphosphonates especially the original alendronate.

All participants had significantly improved in pain reduction during the first visit which might indirectly indicate the rapid onset of the drug on anti-bone resorption and the use of pain medication. However, as there was no significant difference between the use of pain medication before and during the 12-week trial, it could be concluded that the trial drug provided a significant pain improvement in the participants.

Concerning the side effects of the trial drugs,

there were 10/49 participants, 20.4%, experienced minimal side effects during the trial. Most of side effects might not directly relate to the drug, including edema, constipation and abnormal sensation at the lower limbs. Edema is usually related to the use of NSAIDs and constipation usually was the result of the administration of calcium carbonate. There was no clear explanation of the abnormal sensation in one participant in this trial, as alendronate had no direct effect on central and peripheral nervous system. On the other hand, nausea and dyspepsia directly related to alendronate and might be the patients' disturbing side effects of concern when using the drug. These side effects were found in 4/49 participants, 8.2%. Muscle pain could be the result of the changes of serum calcium, which have been reported during the use of common bisphosphonates. However, all side effects were minimal and all participants could tolerate them and complete the trial. Close observation in more participants may be needed when the trial drug is used in the clinic.

Different preparations of alendronate have different in pharmacokinetics, especially the absorption ability, as the drug has slow drug absorption and carries a rather high risk of esophageal irritation[12,13]. The generic drugs in the markets vary in disintegration time, between 14 to 342 seconds[14]. The drugs, which have shorter disintegration time usually, have better drug absorption but they may have higher incidence of GI irritation. The drugs which have longer disintegration time usually have poorer drug absorption but they may have less incidence of esophageal irritation. The original drug has a disintegration time of 86 seconds[15]. The prevalence of esophageal and gastrointestinal complication is around 2-3%, which was comparable to placebo[1,6,8]. In this study, only 3 participants, 6%, experienced these GI side effects, which were directly related to the drug. The incidence of GI side effects of the trial drug was comparable to the original drug[16,17]. The trial drug has fewer efficacies on bone resorption inhibition than its expectation (90% of enrolled participants). Nevertheless, the cost of the treatment was below than 50% of the original regimen. The original regimen, i.e. taking alendronate 70 mg once a week, was widely used in western countries. Besides, there were several regimens for reducing the cost of treatment and shown the effectiveness of bone suppression[18,19]. However, more information about the drug efficacies and safety in terms of suppression period and magnitude of suppression is still needed. This drug might be the one of the optional regimen using for the primary prevention of osteoporotic fractures. A longer-term study for the efficacy of the drug with greater numbers of participants is essential for the calculation of the cost benefit of the drug.

Conclusion

The once-a-week medication of Kaspar's oral alendronate sodium trihydrate (70 mg) could normalize serum bone turnover markers in about 85% of the post-menopausal participants who had high bone turnover. Minimal side effects were found in about 8% of the participants.

Acknowledgement

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Potential conflicts of interest

None.

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ผลของยาอเลนโดรเนตแบบรับประทานสัปดาห์ละหนึ่งครั้งต่อการเปลี่ยนแปลงการหมุนเวียนการทำงานของกระดูก

ลิขิต รักษ์พลเมือง, สารเนตร ไวคกุล

วัตถุประสงค์: *เพื่อศึกษาผลของยาอเลนโดรเนตของบริษัทแคสป้าประเทศไทยในด้านประสิทธิภาพการยับยั้ง การหมุนเวียนของกระดูกรวมถึงความปลอดภัยของยาสำหรับการรับประทานสัปดาห์ละ 1 ครั้ง*

วัสดุและวิธีการ: *อาสาสมัครหญิงที่เข้าสู่วัยหมดประจำเดือนและเป็นโรคกระดูกพรุน จำนวน 49 คน เข้าร่วมโครงการโดยการรับยาสำหรับรับประทานสัปดาห์ละ 1 ครั้งเพื่อรักษาโรคกระดูกพรุน คณะผู้นิพนธ์ได้ทำการวัดผลของยาต่อการหมุนเวียนการทำงานของกระดูกและผลข้างเคียงของยาในครั้งแรกที่พบ อาสาสมัครและในสัปดาห์ที่ 6 และ 12*

ผลการศึกษา: *ผู้ป่วยจำนวน 13 ราย (26.3%) มีผลข้างเคียงในปริมาณน้อยจากยาที่ได้รับประทาน ผู้ป่วยจำนวน 42 ราย (85.7%) มีผลเลือดของ beta crosslab กลับสู่ระดับปรกติ และผู้ป่วยจำนวน 45 ราย (91.8%) มีผล N-MID osteocalcin กลับเข้าสู่ค่าปรกติและไม่มีผู้ป่วยรายใดที่มีค่า P1NP ในระดับต่ำ ผู้ป่วยทุกรายมีค่า alkaline phosphatase ในเลือดต่ำลง*

สรุป: *ยาที่ได้ทำการวิจัยมีผลยับยั้งได้ประมาณ 85 เปอร์เซ็นต์ของผู้ป่วยที่มีภาวะหมดประจำเดือนและมีการหมุนเวียนกระดูกสูงภายใน 12 สัปดาห์ และไม่พบว่ายามีผลข้างเคียงที่รุนแรงในผู้ป่วยที่ได้ทำการวิจัย*