Asian Biomedicine Vol. 6 No. 1 February 2012;
DOI: 10.5372/1905-7415.0601.129

Brief communication (Original)

Safety and efficacy of menatetrenone in children with osteogenesis imperfecta

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Background: Osteogenesis imperfecta (OI) is an inherited connective tissue disorder with defective bone quality leading to increased bone fragility and low bone mass. Menatetrenone has been shown to reduce bone mineral density (BMD) loss as well as the incidence of fractures in patients with osteoporosis.

Objectives: We investigated the effects of menatetrenone in five prepubertal children with OI.

Methods: All patients had been treated with intravenous pamidronate for four to 42 months prior to enrollment in this study. Pamidronate was discontinued at least two months before starting 15 milligrams per day of oral menatetrenone. Menatetrenone was given for 12 months. BMD was measured at baseline and one year after menatetrenone treatment.

Results: During one year of menatetrenone treatment, the incidence of fractures was 1.0 (0.0-2.0) times/year, which was not significantly different from the fracture rate of 1.2 (0.0-1.5) times/year during pamidronate treatment. However, it significantly decreased compared with the fracture rate of 10.4 (2.7-47.6) times/year before pamidronate treatment (P=0.043). After one year of menatetrenone, BMD of lumbar spine and left hip significantly increased in three and two patients, respectively**.** However, one patient showed a significant decrease in BMD in both regions. Noteworthy, none of the patients developed adverse side effects during menatetrenone treatment.

Conclusions: One-year menatetrenone could maintain the decreased fracture rate of intravenous pamidronate in prepubertal OI patients. No adverse effects were observed. Larger and longer studies to determine the benefit of oral menatetrenone as adjunctive treatment in OI patients are warranted.

Keywords: Fracture, menatetrenone, osteogenesis imperfecta, pamidronate

Osteogenesis imperfecta (OI) is an inherited connective tissue disorder with defective bone quality leading to increased bone fragility and low bone mass [1]. It is also known as "brittle bone disease". OI patients suffer multiple fractures even after minimal or no trauma, resulting in bone deformities, scoliosis, and short stature. Severely affected patients may eventually become wheelchair-bound or totally immobilized.

Previous studies revealed bone turnover was significantly increased in children with OI [2]. This provides a rationale for the use of bisphosphonates, stable analogs of pyrophosphates, which are potent inhibitors of bone resorption and bone turnover in OI patients. Although bisphosphonates are currently the most widely used treatment in this condition, none are approved for use in children or adults with OI due to their uncertain long-term efficacy and potential adverse effects. The benefit of bisphosphonates in OI could be demonstrated only during the first two to four years of therapy and the long-term effects remain unknown [3-6]. Moreover, inhibition of bone resorption by bisphosphonates raises concerns about disruption of bone remodeling, which may be adversely affecting bone quality. Therefore, novel treatment for prevention of fractures in OI patients is warranted.

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Vitamin K has been shown to play an important role in bone metabolism [7-8]. Low levels of vitamin K are associated with low bone mineral density (BMD) and increases bone fractures [9-12]. Vitamin K-dependent carboxylation converts glutamyl residues to gamma-carboxy-glutamyl (Gla) residues. This process enhances calcium ion binding of various bone proteins with Gla residues including osteocalcin, the most abundant non-collagenous protein in the bone [13-14]. Menatetrenone, an oral vitamin K2, has been shown to effectively reduce BMD loss as well as the incidence of osteoporotic fractures in patients with advanced osteoporosis [15-18]. There is, however, no published study of menatetrenone treatment in OI patients.

In this study, we prospectively investigated the effects of menatetrenone treatment on BMD, incidence of fracture, and safety in five prepubertal children with OI.

Materials and methods

Five OI patients who were treated at King Chulalongkorn Memorial Hospital were included in this study. All cases were examined by clinical geneticists and a pediatric orthopedic surgeon. All patients had been treated with intravenous pamidronate for four to 42 months prior to enrollment. Pamidronate was then discontinued at least two months before the start of 15 milligrams per day of oral menatetrenone. Menatetrenone was given concomitantly with calcium and vitamin D supplementation for 12 months. This study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University and informed consent was obtained from all participants.

Adverse effects of menatetrenone were monitored throughout the study period. Bone mineral density and blood chemistry were evaluated at baseline and 12 months after menatetrenone treatment. Bone mineral density of the anterior lumbar spine (L2-L4) and the proximal femur were determined by dual energy x-ray absorptiometry (DEXA) on a Discovery A bone densitometer (Hologic Inc., Waltham, MA) expressed as values in g/cm^2. The significance of BMD change over one year was determined if there was any change beyond the 95% confidence level. The least significant change (LSC) at the lumbar spine was 0.008060 g/cm^2, while the change at the left hip was 0.009630 g/cm^2. Incidence of fracture during menatetrenone treatment was evaluated and compared with the fracture rates during and before pamidronate therapy.

Data were presented as median (range) unless otherwise indicated. Differences in parameters before and after treatment were examined using the non-parametric Wilcoxon signed rank test. All data were analyzed using SPSS 14. Statistical significance was defined as P value <0.05, two-sided.

Results

Characteristics of the five recruited patients were summarized in **Table 1**. Incidence of fractures before and during pamidronate treatment in the OI patients was 10.4 (2.7-47.6) times/year and 1.2 (0.0-1.5) times/year, respectively. During the first year of menatetrenone treatment, the incidence of fracture was 1.0 (0.0-2.0) times/year, which was not significantly different from that during pamidronate treatment but significantly decreased compared with that before pamidronate treatment (**Table 2**).

After one year of menatetrenone treatment, BMD of the lumbar spine increased in three patients (case no. 1, 3, and 5). There was no significant change in one case (case no.2), and a significant decrease in the other (case no. 4). Similarly, BMD of the left hip increased significantly in two patients (case no. 2 and 5). However, of the remaining three cases, it significantly decreased in one (case no. 4) but did not change in the other two (**Table 3**).

Table 1. Characteristics of the OI patients.

Case No.	Sex	Age (month)	Weight (kg)	Height (cm)	Age when started pamidronate (month)	Duration of pamidronate therapy (month)
1	M	9	6.4	66	5	4
2	M	17	7.4	66.5	1	16
3	F	32	9.5	82	1	31
4	M	43	11	88	1	42
5	M	57	12.5	92	22	35

Table 2. Incidence of fractures in five OI patients.

Case No.	Incidence of fracture (times/year)		
	Before pamidronate	During pamidronate	During menatetrenone
1	6.6	0.0	1.0
2	47.6	1.5	0.0
3	10.4	1.2	2.0
4	17.4	0.6	1.0
5	2.7	1.4	0.0
Median	10.4	1.2[a]	1.0[a,b]
Max	47.6	1.5	2.0
Min	2.7	0.0	0.0

[a]P=0.043 *vs* before pamidronate, [b]P =0.686 *vs* during pamidronate

Table 3. Bone mineral density of the lumbar spine and the left hip at baseline and after one year of menatetrenone treatment.

Case No.	BMD lumbar spine (g/cm^2)			BMD left hip (g/cm^2)		
	Baseline	1 year	BMD change	Baseline	1 year	BMD change
1	0.190	0.238	+0.048[a]	0.260	0.258	-0.002
2	0.265	0.245	-0.02	0.368	0.444	+0.076[a]
3	0.307	0.363	+0.056[a]	0.327	0.331	+0.004
4	0.489	0.442	-0.047[a]	0.592	0.483	-0.109[a]
5	0.294	0.352	+0.058[a]	0.336	0.402	+0.066[a]
Median	**0.294**	**0.352**[b]		**0.336**	**0.402**[c]	
Max	0.489	0.442		0.592	0.483	
Min	0.190	0.238		0.260	0.258	

[a]significant BMD change, [b]P=0.225 *vs* baseline, [c]P=0.686 *vs* baseline

None of the patients developed adverse effects during menatetrenone treatment. Blood urea nitrogen, serum calcium and serum phosphate did not change after menetetrenone treatment as shown in **Table 4**.

The least significant change (LSC) at the lumbar spine was 0.008060 g/cm^2, while the change at the left hip was 0.009630 g/cm^2. The significance of BMD change over one year was determined if there was any change beyond 95% confidence level.

Table 4. Blood urea nitrogen (BUN), serum calcium and serum phosphate at baseline and after one year of menatetrenone treatment.

Case No.	BUN (mg/dl)		Calcium (mg/dl)		Phosphate (mg/dl)	
	Baseline	1 year	Baseline	1 year	Baseline	1 year
1	11	14	10.3	10.0	5.2	4.7
2	13	12	11.1	11.2	4.8	5.5
3	11	10	10.7	10.8	4.5	3.4
4	15	13	10.1	9.7	4.7	4
5	13	14	10.5	10.1	5.4	4.9
Median	13	13	10.5	10.1	4.8	4.7
Max	15	14	11.1	11.2	5.4	5.5
Min	11	10	10.1	9.7	4.5	3.4

Discussion

In the present study, one-year treatment of oral menatetrenone could maintain the reduced incidence of fractures comparable to that seen during pamidronate treatment and without significant adverse effects. In addition, the fracture incidence during menatetrenone therapy was significantly lower than that seen before pamidronate treatment. Although pamidronate was discontinued at least two months before the initiation of oral menatetrenone, it remains unclear whether the reduced rate of fracture during menatetrenone treatment reflects beneficial effect of menatetrenone itself or a remaining effect of the previous pamidronate therapy [3-4]. Further investigations regarding this issue are warranted.

The overall BMD after one year of menatetrenone therapy showed a non-significant increase. However, one out of five patients had a substantially decreased BMD after menatetrenone treatment (decreased BMD of the lumbar spine and left hip in case no. 4). Given that these pediatric patients were expected to have growing bones and therefore increased BMD over time, we do not know whether the increase of BMD in some patients resulted from menatetrenone, increasing age or both. This remains to be elucidated. Moreover, this also indicates that menatetrenone might have different effects on different OI patients.

In contrast to our findings, reports in osteoporotic patients showed increased BMD after menatetrenone treatment [15-18]. The discrepancy between our findings and previous studies in osteoporotic patients may have resulted from the difference in vitamin K status between these two populations and the underlying disease mechanism.

Bisphosphonates have been repeatedly shown to effectively increase BMD in OI patients [3-5, 19]. Unfortunately, they could not normalize BMD and their effects on fracture rates were not consistently demonstrated. Therefore**,** bisphosphonates could be considered an effective but not sufficient therapy in OI patients. Since bisphosphonates primarily work by inhibition of bone resorption, additional therapy with other drug classes that could effectively enhance bone formation, such as menatetrenone, would be beneficial.

In conclusion, menatetrenone in combination with calcium and vitamin D supplementation seems to be an insufficient treatment to increase BMD and probably could not effectively reduce fracture rates in OI patients in the long term. However, given the importance of vitamin K in bone health and the negligible adverse effects of this drug, menatetrenone should be considered as adjunctive therapy, especially in OI patients who are at risk of vitamin K deficiency. Combination of menatetrenone and pamidronate would be another interesting potential treatment regimen for OI patients.

Acknowledgements

We would like to thank the patients and their families for participation in this study. This study was supported by the Thailand Research Fund, the National Center for Genetic Engineering and Biotechnology and the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission (HR1163A). The authors declare no conflict of interest in conducting this study.

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