

Intravenous pamidronate compared with oral alendronate for the treatment of postmenopausal osteoporosis

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ABSTRACT

There are several options for the treatment of osteoporosis in postmenopausal women.

One of the options is treatment with bisphosphonates, which are very potent inhibitors of osteoclast-mediated bone resorption *in vitro* and *in vivo*. The most potent bisphosphonates have a nitrogen side chain and can be given orally or intravenously (*i.v.*). In the present study we evaluated retrospectively the effect of intravenously administered pamidronate (60 mg monthly) in comparison with oral alendronate with regard to bone mineral density (BMD) and vertebral fractures.

A total of 117 consecutive women aged 46 to 78 years were seen in the outpatient clinic because of postmenopausal osteoporosis. Three-year follow-up data were available for a total of 45 patients treated with pamidronate *i.v.* and 40 patients on alendronate for at least three years. In the pamidronate group mean T score of lumbar spine BMD increased from -3.49 ± 0.72 to -2.81 ± 0.74 SDs after three years of treatment ($p < 0.001$). In the 40 patients treated with alendronate we observed an increase in the T score from -2.95 ± 0.67 to -2.33 ± 0.74 SDs ($p < 0.001$) during the same observation period.

X-rays of the lumbar and thoracic spine were analysed from 25 patients in each group who had been treated for at least three years. At baseline nine patients (36%) in the pamidronate group had one or more vertebral fractures compared with seven patients (28%) in the alendronate group. After three years of treatment no new fractures were observed, while only three women in the pamidronate

group and two in the alendronate group showed a deterioration of one or more pre-existing vertebral fractures ($p = ns$ between groups).

This retrospective analysis demonstrates that monthly intravenous administration of pamidronate is at least as good as alendronate taken orally in the treatment of women with postmenopausal osteoporosis, with regard to improvement of bone mineral density of the lumbar spine. We conclude that it is a good alternative for the more widely used oral bisphosphonates as it is effective, well-tolerated and easy to administer.

INTRODUCTION

Postmenopausal osteoporosis is a major healthcare problem that results in substantial morbidity and mortality.¹⁻⁴ Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.¹

During adult life, bone is continuously remodelled, resorbed by osteoclasts and new bone formed by osteoblasts. In young adults remodelling is near-perfectly coupled so that the overall rate of resorption is almost exactly matched by the overall rate of formation. Following the menopause, however, the volume of bone resorbed exceeds the volume of new bone formed, leading to osteopenia and osteoporotic disease. Progressive bone loss is almost universal in women after the age of 35 years. The rate of loss is accelerated during

the early postmenopausal period, particularly at skeletal sites with a high proportion of trabecular bone. As a consequence, women have an average lifetime risk of approximately 50% for developing at least one osteoporotic fracture and a risk of 15% for experiencing a hip fracture.^{5,6} These fractures are associated with a high morbidity and a high mortality, as well as a marked reduction in the quality of life and high costs of treatment. There are several options for the treatment of osteoporosis in postmenopausal women. Compounds that inhibit bone resorption, i.e. osteoclastic activity, are attractive pharmacological candidates. One of the options is treatment with bisphosphonates. These are analogues of inorganic pyrophosphate and very potent inhibitors of osteoclast-mediated bone resorption *in vitro* and *in vivo*.⁷ The most potent bisphosphonates have a nitrogen molecule in the side chain (e.g. pamidronate and alendronate) and can be given orally or intravenously (i.v.). Oral administration may cause serious side effects, especially in the digestive system.⁸⁻¹⁰ Although there are several risk factors for fractures, reduced bone mineral density (BMD) is the strongest predictor.¹¹ Thus, one of the goals of pharmacological treatment in women with postmenopausal osteoporosis is to reduce the risk of fractures by increasing bone mass of normal quality. Most of the clinical studies with bisphosphonates have investigated the abilities of a specific compound with regard to inhibition of mineral loss and fracture incidence in comparison with placebo. Almost all known bisphosphonates show more or less advantages with regard to the previously mentioned parameters if compared with placebo treatment or just calcium (and sometimes vitamin D) supplements. Intermittent intravenous regimens with bisphosphonates are being explored as alternatives to oral regimens. In the present study we evaluated retrospectively the effect of i.v. administered pamidronate in comparison with oral alendronate with regard to BMD and vertebral fractures. The decision to start therapy was made by the treating physician together with the patient in the outpatient clinic, so this paper describes the effects of these treatments in real life. Intravenous pamidronate was chosen because some patients prefer this way of administration, because it is easy to administer and avoids (worsening of) gastrointestinal complaints or gastrointestinal side effects of oral bisphosphonates. Furthermore, experiences from clinical practice as well as one paper¹² have suggested that intravenous pamidronate may lead to more rapid reduction in pain.

METHODS

Study population

A total of 117 consecutive women aged 46 to 78 years were seen in the outpatient clinic because of postmenopausal osteoporosis. The same physicians (A.C. Heijckmann and

J.R. Juttmann) followed all patients in one hospital. The diagnosis was based on BMD measurements of the lumbar spine, while other causes of osteoporosis were excluded. We used the criteria of the World Health Organisation,¹³ so all patients had a BMD value more than 2.5 SD below the adult peak bone mass. They were started on i.v. pamidronate (n=67) or alendronate (n=50), and continued this therapy for at least one year. At the start of treatment all patients were at least five years postmenopausal. Pamidronate was given to patients primarily if no daily oral medication was desired or needed, and also to some subjects who experienced gastrointestinal side effects after a short one to three weeks' period of alendronate use and to patients who experienced severe low back pain. None of the women were on hormone replacement therapy (HRT) during this study. Due to the retrospective nature of our study, previous HRT use could not be ascertained fully.

Oral calcium supplements were given (500-1000 mg/day) if the dietary history indicated that daily calcium intake was less than 1000 mg. No other medication with a possible effect on bone metabolism (e.g. vitamin D, corticosteroids) was used. Vitamin D levels were not measured routinely before or during this treatment.

Treatment

Patients in the pamidronate group received 60 mg of this drug by intravenous infusion once monthly. Pamidronate was dissolved in 500 ml saline, which was infused over a period of three hours in an outpatient clinic setting. Patients on alendronate took one 10 mg tablet orally once a day, in the morning, 30 minutes before breakfast.

Endpoints

Our clinical protocol describes that BMD of the lumbar spine is measured yearly with a Hologic 2000 BMD measuring machine following standard procedures. X-rays of the spine were also taken every year. In July 2001 we retrospectively evaluated the data of all patients who had been treated for osteoporosis in our clinic with alendronate or pamidronate i.v. during the last five years. An aselect sample of 25 patients from each group was drawn to assess lumbar and thoracic spine X-rays and evaluate possible new vertebral fractures. A vertebral fracture at baseline was defined as a reduction of either the posterior, anterior or middle height of the vertebra of at least 20% with an absolute infraction of 4 mm compared with one of the adjacent vertebra. A new fracture was defined as a reduction of at least 20% with an absolute decrease of at least 4 mm of either the posterior, anterior or middle height of the same vertebra at baseline.

Statistical analysis

A descriptive statistics report was created using SPSS (version 11.01 for Windows™). Independent two tailed t-tests

were performed to test for significance between the two groups (pamidronate versus alendronate). Analyses for trend and paired t-tests were performed to test for the significance level within the group, testing interval 0 versus 1, 2 and 3. P values <0.05 were considered to be statistically significant.

RESULTS

Table 1 depicts some of the baseline data. Full data were available for a total of 45 patients who were treated with pamidronate i.v. for at least three years. Their mean age at start was 66.6 ± 8.4 years and their average BMD at the lumbar spine was 0.69 ± 0.08 g/cm². The 40 patients who were treated with alendronate for at least three years were slightly younger (age 61.2 ± 9.9 years), and had a slightly higher BMD (0.75 ± 0.07 g/cm², p<0.05 versus the pamidronate group).

The mean T score had increased by 0.67 (from -3.49 ± 0.72 to -2.81 ± 0.74) after three years of treatment in the pamidronate group (p<0.001). The alendronate-treated patients showed an increase of 0.62 (from -2.95 ± 0.67 to -2.33 ± 0.74, p<0.001) during the same observation period (table 2).

As there was a difference in BMD at baseline between the two groups, we also assessed the percentual change over time, which was not different between the two groups (figure 1).

Table 1
Baseline characteristics of the patients with a complete three-year follow-up

	PAMIDRONATE	ALENDRONATE
Number	45	40
Age	66.6 ± 8.4*	61.2 ± 9.9
BMD lumbar spine (g/cm ²)	0.69 ± 0.08*	0.75 ± 0.07
T score (SDs)	-3.49 ± 0.72*	-2.95 ± 0.67

* P<0.05 pamidronate versus alendronate.

Table 2
BMD and T scores in the pamidronate-treated (n=45) and the alendronate-treated group (n=40), observation period up to three years

	START		THREE YEARS	
	PAMIDRONATE	ALENDRONATE	PAMIDRONATE	ALENDRONATE
BMD	0.69 ± 0.08*	0.75 ± 0.07	0.77 ± 0.08* [§]	0.82 ± 0.08 [§]
T score	-3.49 ± 0.72*	-2.95 ± 0.67	-2.81 ± 0.74* [§]	-2.33 ± 0.74 [§]
Delta T	-	-	0.67 ± 0.35 [#]	0.62 ± 0.37
Increase BMD in %	-	-	11.6 ± 6.5 [#]	9.3 ± 5.8

* P<0.05 pamidronate versus alendronate, # p=ns pamidronate versus alendronate, § p≤0.001 three years versus start.

Additional analysis of the cohort of patients who completed four years of treatment indicates that both patient groups showed a further small increase in BMD from year 3 to year 4. In 20 patients on pamidronate mean BMD increased from 0.76 ± 0.07 g/cm² to 0.78 ± 0.07 g/cm², and in the 19 subjects on alendronate it increased further from 0.78 ± 0.10 g/cm² to 0.80 ± 0.10 g/cm² (both p<0.001).

X-rays of the lumbar and thoracic spine were analysed from 50 patients treated for at least three years (25 in each group). At baseline nine patients (36%) in the pamidronate group had one or more vertebral fractures compared with seven patients (28%) in the alendronate group. After three years of treatment only three women in the pamidronate group and two in the alendronate group showed a deterioration of one or more pre-existing vertebral fractures. There were no new fractures in either group (table 3).

Pamidronate was well tolerated. A few patients developed the expected flu-like symptoms, but only from the first administration of the drug.

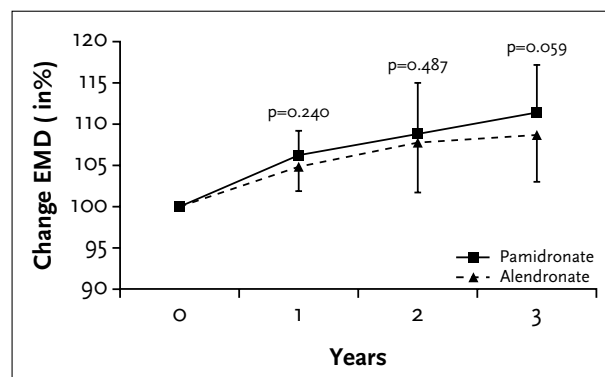


Figure 1
Percentage change BMD (pamidronate versus alendronate)
There was no significant difference between the two treatment groups. However, there was a statistical difference (p≤0.001) in BMD increase between every year in the same group.

Table 3
Fracture incidence in both groups

	NUMBER ANALYSED	NUMBER WITH VERTEBRAL FRACTURES AT BASELINE	NUMBER WITH DETERIORATION OF FRACTURES AFTER THREE YEARS	NEW FRACTURES
Pamidronate	25	9 (36%)*	3	0
Alendronate	25	7 (28%)	2	0

* $P=ns$.

DISCUSSION

This analysis demonstrates that monthly intravenous administration of pamidronate is at least as good as alendronate taken orally in the treatment of women with postmenopausal osteoporosis, with regard to improvement of bone mineral density of the lumbar spine. We observed an increase in BMD of 11.6% in the pamidronate group compared with 9.3% in the alendronate group, which is not statistically significant. Possibly this difference can be explained by a lower baseline BMD of the pamidronate group. The increase in BMD corresponds well with data described in the literature on the general effects of the more frequently used oral bisphosphonates. For alendronate the average was 9% after three years of treatment.¹⁴ Reid *et al.* found an increase in lumbar spine BMD of 9.4% in 48 postmenopausal women treated with pamidronate 150 mg/day orally.¹⁵ In a recent Dutch study in 78 postmenopausal women and 23 men with at least one vertebral fracture, an increase of 14.3% of BMD of the spine was found after five years of treatment with oral pamidronate.¹⁶ Only limited results of intravenous administration of pamidronate are available. Also, several different doses, regimens and intervals were employed,^{17,18} which makes the comparison of these studies difficult. Krieg *et al.* treated 11 patients with intravenous pamidronate (60 mg every three months) for osteoporosis after heart transplantation (mean BMD 0.809 ± 0.017 g/cm³), and showed an increase in BMD at the lumbar spine of 14.3% after three years of treatment.¹⁷ Younes *et al.* treated 20 patients with osteopenia and osteoporosis with 30 mg pamidronate intravenously every three months and found a significant increase in bone mineral density after 14 months.¹⁹ In our small group of patients for whom a four-year follow-up was available, we still found a small increase in BMD between year 3 and 4, in both groups. A similar continued positive effect of bisphosphonates was previously reported by Tonino *et al.* who found a still further increase in BMD amounting 0.8% a year, even in years 5 and 6.²⁰ No striking difference in fracture incidence was noticed between the two groups before and during treatment, although we realise that the groups investigated are too small to draw firm conclusions on this aspect.

In the FIT (Fraction Intervention Trial) study²¹ the effect of alendronate on fracture incidence was studied. A new vertebral fracture was defined as a decrease of 20% and at least 4 mm in the height of any vertebral body from baseline to end of the study. In the group with existing vertebral fractures at baseline they found an annual incidence for a radiological vertebral fracture from 2.61% in the alendronate group versus 5.01% in the placebo group. In our present study, after three years of treatment we did not find any new fractures; in 12% of pamidronate users a deterioration of fractures was seen compared with 8% in the alendronate group.

We conclude that intravenous administration of pamidronate is a good and attractive alternative for the more widely used oral bisphosphonates, as it is effective, well-tolerated and easy to administer. We are currently performing a prospective evaluation of this treatment with a more systematic evaluation of pain symptoms.

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