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Primary Prevention of Glucocorticoid-Induced Osteoporosis with Intermittent Intravenous Pamidronate: A Randomized Trial

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Abstract. The aim of this study was to assess whether early intermittent I.V. administration of disodium pamidronate can effectively achieve primary prevention of glucocorticoid-induced osteoporosis (GIOP). A total of 27 in- or outpatients who required first-time, long-term corticosteroid therapy at a daily dose of at least 10 mg prednisolone were studied. Patients were randomly selected to receive either pamidronate and calcium or calcium alone. Patients allocated to pamidronate treatment (pamidronate group) received a first intravenous infusion of 90 mg pamidronate simultaneously with the initiation of their steroid treatment. Subsequently, they received 30 mg pamidronate, intravenously, every 3 months, for as long as steroid therapy was continued. As with the control patients (calcium group), they were put on a daily 800-mg elemental calcium supplement given as calcium carbonate. Lumbar spine and hip (total and subregions) bone mineral densities (BMDs) were measured at the start and every 3-months by dual-energy X-ray absorptiometry (Hologic® QDR-2000). Over 1 year, the pamidronate group showed a significant BMD increase in the lumbar spine (3.6%), and at all sites of the hip (2.2% at the femoral neck). In the calcium group, a significant BMD reduction was registered at the lumbar spine (−5.3%) and at the femoral neck (−5.3%). Differences between the groups were significant at all sites measured. Intermittent intravenous pamidronate effectively achieves primary prevention of GIOP, as assessed by BMD measurements over 1 year.

Key words: Osteoporosis — Bisphosphonates — Pamidronate — Glucocorticoids — Bone mineral density.

Osteoporosis is the most common complication in patients who require chronic glucocorticoid treatment. Glucocorticoid-induced osteoporosis (GIOP) results from both a depressed osteoblastic and an enhanced osteoclastic activity as well as from a reduced intestinal calcium absorption, increased renal calcium excretion, and disturbances in metabolism of vitamin D and gonadal hormones [1–3]. GIOP is a serious condition, with an overall fracture rate higher than 40% in patients requiring long-term use of glucocorticoids [4]. Focusing on hip fracture, Cooper et al. [5] found a relative risk of 2.7 for current corticosteroid therapy, as compared with a control population. Numerous treatments such as calcium [6], vitamin D metabolites [7], calcitonin [8], estrogens [9], testosterone [10], fluoride [11], or bisphosphonates [12–23] have been evaluated to treat or minimize GIOP. Deflazacort, a novel steroid with some bone-sparing properties, has also been tested [24]. However, most clinical trials only deal with either curative treatment, i.e., after fractures have already occurred or with secondary prevention, i.e., after low bone density has developed, but fractures have not yet occurred [25]. Because significant bone loss starts very early [26–29], GIOP treatment should be initiated as soon as corticosteroid therapy begins (primary prevention).

Bisphosphonates are potent inhibitors of bone resorption. This property has been used to counteract the deleterious effects of glucocorticoids on bone. Etidronate [12–17], clodronate [18], pamidronate [19–21], alendronate [22], and risedronate [23] have been used in the treatment or secondary prevention of GIOP with favorable results. As yet, only one study has addressed the issue of primary prevention with encouraging results, as far as BMD was concerned, with cyclical etidronate administered to 20 postmenopausal women on high doses of prednisolone [15].

The present work was undertaken to assess the capability of pamidronate which has proved to be potent and safe [30] for achieving effective primary prevention of GIOP, by starting its administration concomitantly with the onset of a high-dose steroid therapy.

Patients and Methods

We initially enrolled 32 in- or outpatients expected to require long-term, high-dose glucocorticoid therapy. Most of the selected patients had inflammatory rheumatic diseases. Patients previously treated with either glucocorticoid, fluoride, or bisphosphonate were not eligible, nor were those with renal failure, urolithiasis, hyperparathyroidism, malignancy, or liver or thyroid disease.

In order to receive either pamidronate and calcium or calcium alone, patients were randomized by minimization (according to the method described by Pocock and Simon [31], using a personal computer software), taking into account the starting dose of steroid (prednisolone, 10–80 mg/day), sex, pre- or postmenopausal status, with (ERT+) or without (ERT−) estrogen replacement therapy.

Simultaneously with the initiation of steroid therapy, patients in the pamidronate group received an intravenous infusion of pamidronate (Aredia®, Ciba-Geigy, Basle, Switzerland), 90 mg in 500 ml NaCl 0.9% over 4 hours. Subsequently, every 3 months they received a 30-mg dose, in 250 ml NaCl 0.9% over 30 minutes, for as long as steroid therapy was continued. As with control patients, they were put on a daily 800-mg elemental calcium supplement given as calcium carbonate. This intermittent intravenous regimen

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Table 1. Baseline characteristics of the 27 patients available for analysis

Treatment group	Pamidronate	Calcium
N	14	13
Males/Females	3/11	2/11
Premenopausal	1	2
Postmenopausal (ERT +)/(ERT −)	3/7	2/7
Conditions		
Polymyalgia rheumatica	4	5
Temporal arteritis	3	2
Rheumatoid arthritis	3	3
Other	4[a]	3[b]
Age (years)	60 ± 16 [63][c]	61 ± 12 [64]
Body mass index	24.9 ± 4.0 [24.3]	22.7 ± 4.0 [21.6]
Initial steroid dosage (prednisolone mg/day)	31.2 ± 23.8 [17.5]	28.1 ± 23.8 [15.0]
Initial BMD measurements (g/cm^2)		
L1-L4	0.857 ± 0.118 [0.820][c]	0.960 ± 0.161 [0.965]
Femoral neck	0.716 ± 0.105 [0.713]	0.713 ± 0.124 [0.731]
Total hip	0.779 ± 0.118 [0.760]	0.800 ± 0.144 [0.830]
Trochanter	0.589 ± 0.110 [0.551]	0.622 ± 0.135 [0.633]
Intertrochanter	0.912 ± 0.134 [0.892]	0.925 ± 0.158 [0.960]
Ward's triangle	0.537 ± 0.147 [0.495]	0.568 ± 0.129 [0.564]

[a] Hemolytic anemia; inflammatory bowel diseases (2×); asthma
[b] Uveitis; sarcoidosis, reactive arthritis
[c] Mean ± SD [median]

was adapted from Gallacher et al. [21]. A loading dose of 90 mg pamidronate was given with the prospect of matching the highest dose required at the time of initiating glucocorticoid therapy.

Lumbar spine, hip, and hip subregions (total hip, neck, trochanter, intertrochanter, and Ward's triangle) bone mineral densities (BMDs) were measured at the start and at 3-month intervals thereafter. BMDs were measured by dual-energy X-ray absorptiometry (Hologic® QDR-2000). The first BMD measurement was always carried out immediately before the start of the glucocorticoid therapy or at the latest, within the first week. In our hands, the coefficient of variation of the technique amounts to 0.82% at the spine, 0.75% at the total hip, and 0.79% at the femoral neck [32].

Together with routine laboratory tests, 24-hour urine calcium, creatinine, and sodium measurements were performed at the beginning of the study and repeated every 3 months. Baseline serum calcium, phosphorus, and $25OHD_3$ levels were within the normal range. No significant difference was observed between the two groups.

One of the authors (YB) took the medical history and made a clinical examination every 3 months. Lateral X-rays films of the thoracic and lumbar spine were obtained at the start and at 12 months in order to detect any asymptomatic vertebral fracture, and to measure the spine deformity index according to the method of Minne et al. [33]. Additional X-ray studies were performed in patients with acute thoracic or lumbar spine symptoms in order to detect vertebral fractures.

Monitoring and treatment continued for every patient of both groups as long as he or she was taking at least 5 mg prednisolone daily.

The study protocol was approved by the Ethics Committee of the Louvain University Hospital in Mont Godinne. All patients gave their written informed consent.

Statistics

Numerical results are expressed as means ± SD and by medians unless otherwise specified. Since the number of available results at various times was different, the effect of treatment and time on BMD measurements was studied by regression analysis of repeated measures using generalized estimating equations [34] with the RMGEE program [35]. This procedure is a variant of multivariate linear regression, which takes into account the fact that results of a particular patient at different times are not independent. On the one hand, explanatory variables tested were treatment and linear and quadratic time effects on the whole group, and on the other hand, linear and quadratic effects of time in each treatment group separately. Group characteristics were compared by the Student's *t* test.

Results

Of the 32 patients initially enrolled, 5 dropped out during the first 3 months. One patient died of severe pulmonary infection (calcium group), another no longer required glucocorticoids after 6 weeks, and 3 patients (calcium group) did not keep their appointment. Baseline characteristics of the 27 remaining patients available for analysis appear in Table 1. Patient groups did not differ with respect to clinical data, daily and cumulative steroid dosage, or baseline BMD measurements. All the patients received at least 10 mg prednisolone daily during the first 3 months. The cumulative steroid dosages are shown in Table 2. There were no significant differences between the two groups over the entire study period.

Changes in Bone Mineral Density

Table 3 shows lumbar spine and femoral neck BMD measurements expressed as percentages of initial values at 3, 6, 9, and 12 months. Mean follow-up was 12.2 ± 6 months for the 14 patients in the pamidronate group and 10.5 ± 6.5 months for the 13 patients in the calcium group (NS).

Table 4 gives regression coefficients of time variables i.e., generalized estimating equations (GEE) in each group and the comparison between treatment groups at each measurement site. Graphic representations of these equations (lumbar spine and femoral neck) are shown on Figure 1. It can be seen that they fit in with the observed BMD measurements at 3, 6, 9, and 12 months.

Table 2. Cumulative steroid dosages at study completion, expressed as mg prednisolone (mean ± SD [median])

	Pamidronate group	Calcium group	*P*
3 months	1592 ± 803 [1252]	1674 ± 922 [1320]	NS
6 months	2912 ± 1694 [1900]	2236 ± 708 [1894]	NS
9 months	3953 ± 2323 [2630]	2969 ± 991 [2539]	NS
12 months	5726 ± 2798 [4960]	4027 ± 1195 [3924]	NS

Table 3. BMD measurements at 6 and 12 months expressed as % of initial values (mean ± SD)

	Pamidronate group		Calcium group			
Months	n	L1-L4 BMD	Femoral neck BMD	n	L1-L4 BMD	Femoral neck BMD
3	14	102.14 ± 3.17	101.62 ± 3.01	13	96.94 ± 3.17	98.83 ± 3.64
6	12	101.90 ± 2.49	102.54 ± 3.90	9	96.16 ± 5.68	95.86 ± 4.91
9	10	103.53 ± 2.02	101.57 ± 4.22	6	96.28 ± 4.03	94.25 ± 5.78
12	9	103.94 ± 2.60	102.96 ± 6.42	4	93.99 ± 2.58	95.87 ± 6.05

Table 4. Changes in bone mineral density (expressed as regression coefficients of time[a] variables in each group) and comparison between treatment groups at each site

		Time $\beta_1 \pm SE$ (β_1)	Significance	$(Time)^2/1000$ $\beta_2 \pm SE$ (β_2)	Significance	Treatment comparison
L1–L4	Pamidronate	0.016 ± 0.003	$P < 0.001$	−0.016 ± 0.007	$P = 0.015$	$P < 0.001$
	Calcium	−0.026 ± 0.008	$P < 0.001$	0.031 ± 0.012	$P = 0.009$	
Neck	Pamidronate	0.014 ± 0.007	$P = 0.029$	−0.023 ± 0.009	$P = 0.009$	$P = 0.002$
	Calcium	−0.025 ± 0.010	$P = 0.007$	0.030 ± 0.015	$P = 0.040$	
Total hip	Pamidronate	0.013 ± 0.005	$P = 0.004$	−0.022 ± 0.007	$P < 0.001$	$P < 0.001$
	Calcium	−0.018 ± 0.007	$P = 0.018$	0.022 ± 0.013	NS ($P = 0.085$)	
Trochanter	Pamidronate	0.019 ± 0.007	$P = 0.010$	−0.028 ± 0.011	$P = 0.010$	$P = 0.025$
	Calcium	−0.016 ± 0.013	NS	0.020 ± 0.019	NS	
Intertrochanter	Pamidronate	0.015 ± 0.004	$P < 0.001$	−0.025 ± 0.006	$P < 0.001$	$P = 0.002$
	Calcium	−0.014 ± 0.009	NS	0.017 ± 0.014	NS	
Ward's triangle	Pamidronate	0.018 ± 0.008	$P = 0.029$	−0.036 ± 0.014	$P = 0.008$	$P = 0.035$
	Calcium	−0.009 ± 0.008	NS	−0.001 ± 0.016	NS	

[a] Time variables are expressed as days

Table 5 shows the cumulative percentages of BMD changes at 6 and 12 months according to the regression models. The significant BMD increase amounts to 3.6% at the lumbar spine and 2.2% at the femoral neck in the pamidronate group over 1 year. In the calcium group, the significant BMD decline occurring over 1 year amounts to −5.3% at the lumbar spine and −5.3% at the femoral neck. The resulting cumulative differences between the pamidronate and calcium group are also given at each measurement site.

Looking at each group's results, a slowing down effect of the BMD changes appears during the 6–12 month period as compared with the first 6-month period (lumbar spine, femoral neck, and total hip).

X-Rays

During the entire follow-up, one atraumatic vertebral fracture was observed. It happened in a postmenopausal patient, without ERT, in the calcium group, after 6 months of treatment. Apart from this, spine deformity indices measured at 1 year according to the method of Minne et al. [33] showed no significant changes in either study group (data not shown).

Adverse Effects

Pamidronate infusions were well tolerated. No patient suffered from fever, myalgias, etc. No case of thrombophlebitis at the infusion site was observed. Two patients (one in the pamidronate group and one in the calcium group) developed mild hypercalciuria, which responded to a low sodium diet. No other relevant changes were observed in the routine 3-month laboratory measurements.

Discussion

Lukert and Raisz [1] regard bone loss with resulting fractures as the most incapacitating sequelae of steroid therapy.

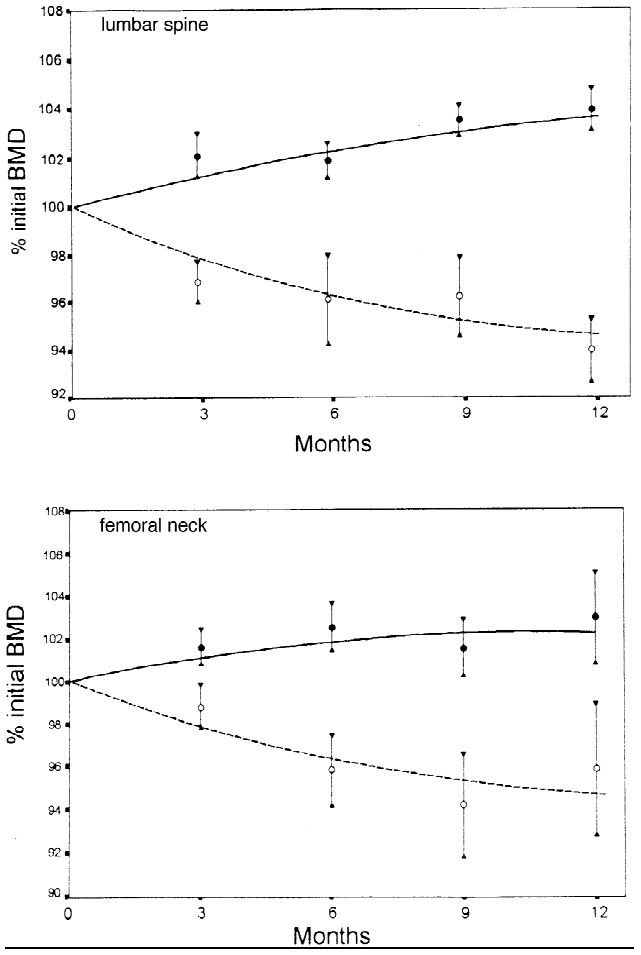

Fig. 1. Lumbar spine BMD changes expressed as % of initial values (upper panel). Observed BMD measurements (means ± SEM) at 3, 6, 9, and 12 months in the pamidronate group (●) and in the calcium group (○). Equations of regression models in function of time (t): pamidronate group: % BMD = 100 ± 0.016 t − 0.016 t^2/1000; calcium group: % BMD = 100 − 0.026 t + 0.031 t^2/1000. Femoral neck BMD changes expressed as % of initial values (lower panel). Observed BMD measurements (means ± SEM) at 3, 6, 9, and 12 months in the pamidronate group (●) and in the calcium group (○). Equations of regression models in function of time (t): pamidronate group: % BMD = 100 ± 0.014 t − 0.023 t^2/1000; calcium group: % BMD = 100 − 0.025 t ± 0.030 t^2/1000.

Several recommendations are commonly made, such as using the lowest effective steroid dose and inhaled forms, screening for low testosterone levels to be corrected in men, and resorting to estrogen replacement therapy in postmenopausal women. These are sensible precautions, but they are restricted to a minority of patients and have mostly proved disappointing.

In a recent review on behalf of a UK Consensus Group Meeting on Osteoporosis, Eastell [25] emphasizes the lack of reliable data in primary prevention. Most of the available studies were carried out as a treatment of established osteoporosis, or as a secondary prevention for further fractures. Clear guidelines for the management of the individual patient at the time of initiating glucocorticoid therapy are not yet available. Taking into account excessive bone resorption, one of the important mechanisms causing GIOP [1–3], bisphosphonates offer a promising approach for primary prevention therapy because of their anti-osteoclastic properties.

In the present primary prevention study, the magnitude of BMD gain we obtained is comparable to the results of the various regimens used in other bisphosphonate trials conducted in the setting of GIOP [12–23]. All of them were also performed over a 1-year study period except for three trials which provide some additional data on a second year follow-up [16, 20, 23].

Etidronate has been administered orally, either continuously [12] or as an intermittent cyclical therapy (15 days out of every 12–14 weeks) [13–17]. In two of these trials, patients were concomitantly given vitamin D supplements [12, 16]. Pamidronate has been used orally [19, 20] with encouraging results, and by intermittent intravenous infusions in an open pilot study [21]. Clodronate has been administered orally with dose-dependent results [18], with only the highest dosage inducing a significant gain in both lumbar and hip BMD. Risedronate has been given orally, either continuously or cyclically, with some BMD gain at the lumbar spine and the trochanter in the continuous administration group [23].

Efficacy at the hip as well as at the lumbar spine should obviously be an important requirement for any prophylaxis regimen in GIOP where hip fracture risk is particularly increased [5]. This was measured in six out of the abovementioned trials [14, 16–18, 21, 23], and a significant BMD gain was demonstrated in four of them [16–18, 23], as well as in our study.

Oral administration of bisphosphonates has generally been reported as fairly well tolerated, except in the clodronate high-dose group [18]. As for oral pamidronate, a recent study of bone mass in nonglucocorticoid-treated rheumatoid arthritis [36] confirms these authors' previous experience, with about 25% of nausea and vomiting, at the 300 mg daily dose leading to early study withdrawal. Also, bisphosphonates, including the more recent ones, should be taken on an empty stomach 30 minutes before consumption of food or beverage, which may present some problems. The intravenous route therefore ensures optimal compliance, and brings appreciated relief to the glucocorticoid-treated patients already receiving an array of drugs that strain their gastrointestinal tract.

We selected pamidronate because of its high activity-to-toxicity ratio [30], especially as to the risk of impaired mineralization at the currently used dose. Although given intravenously, no acute phase-like response (fever, skeletal pain) was observed in our patients. One may wonder whether this type of side-effect, which is known to occur in up to 25% of cases at the first administration, could have been obliterated by glucocorticoid treatment.

Only one other work [15] has so far addressed the important issue of primary prevention as defined above, which our study was specifically aimed at. In both trials, patients initially required first-time, high-dose glucocorticoid treatment. These authors did not measure BMD changes at the hip. Our findings (Table 5) show that, with 3-month intervals of pamidronate dosages the differences in BMD between the pamidronate group and the calcium group at 12 months amounts to 8.9% and 7.5% at the lumbar spine and the femoral neck, respectively. Thus, initiating an adequate bisphosphonate regimen at the same time as the patient's first exposure to prednisolone can not only counteract entirely glucocorticoid-induced bone loss but also provoke some bone gain. This is of great interest, as it is widely

Table 5. Cumulative % of BMD changes at 6 and 12 months according to the regression models

	Pamidronate group		Calcium group		Difference[a]	
	6 months (%)	12 months (%)	6 months (%)	12 months (%)	6 months (%)	12 months (%)
L1-L4	2.4	3.6	−3.7	−5.3	6.1	8.9
Femoral neck	1.9	2.2	−3.7	−5.3	5.6	7.5
Total hip	1.7	1.9	−2.5	−3.4	4.2	5.3
Trochanter	2.6	3.3	−2.2	−3.1	4.8	6.4
Intertrochanter	1.8	2.0	−2.0	−2.8	3.8	4.8
Ward's triangle	2.2	2.0	−2.4	−1.6	4.6	3.6

[a] Difference between pamidronate and calcium group

accepted [26–29] that the rate of bone loss is especially rapid early (within the first 6–12 months) in the glucocorticoid treatment. If unopposed, this massive loss will be all the more difficult to restore, even partly, and will leave the patient with a lifetime risk, whether he is to be treated further with lower-dose glucocorticoid therapy or retreated in times of exacerbation of his chronic or relapsing disease.

In the calcium group, a faster rate of bone loss was observed over the first 6 months as compared with the following 6 months, which conforms with the rapidity of bone loss observed by others at initiation of steroid therapy [26–29]. On the other hand, in our pamidronate group, bone mass increased more slowly during the second 6-month period as compared with the first 6-month period. It seems unlikely that the less dramatic change in BMD in the second 6-month period could be related to the lowering of the pamidronate dosage, which was kept constant after the first ''loading'' perfusion. Intermittent therapy with pamidronate is well known to induce nonlinear increase of BMD [37]. This tailing away pattern has been noted in other bisphosphonate trials whether they were administrated continuously or intermittently [16, 20, 23]. Thus, another argument for the use of a primary prevention strategy, as far as bisphosphonates and other antiresorptive agents are concerned, lies in this leveling-off effect which leads to an attenuating gain in bone mass concurrently with the decreasing number of resorption sites which are put to rest [38]. Therefore, the strongest antiresorptive action of a bisphosphonate regimen should be initiated at the very beginning of the patient's exposure to steroids, when bone is lost at the fastest rate. We believe that primary prevention is the best way to thwart the development of GIOP and to prevent its disastrous consequences.

A strategy of watchful waiting is no longer acceptable in patients submitted to high glucocorticoid doses. We would tend to advocate the possible use of a primary prevention regimen similar to the one we studied, in patients who are treated from the outset with low-dose glucocorticoids, as it has recently been shown that any daily dose above 4 mg prednisolone [39] induces significant bone loss. Our findings warrant exploring this approach.

Conclusion

With a very significant BMD increase over 1 year at both the lumbar spine (3.6%) and the femoral neck (2.2%) in the pamidronate group, and a highly significant difference between pamidronate and control groups at all measurement sites, our data indicate that early administration of intravenous pamidronate effectively protects against the rapid bone loss during the first months of glucocorticoid therapy. Clearly, longer follow-up on a larger number of patients would be required to confirm that bone gain measured as BMD translates into a clinically relevant reduction in fracture rate.

Intravenous administration of pamidronate is a simple, safe, and effective means to achieve primary prevention of glucocorticoid-induced osteoporosis. The 3-month intravenous regimen ensures optimal compliance and is also perfectly suited to outpatients.

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