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Perspective Article

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Long term effects of a single dose of intravenous Ibandronate

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Abstract

For defining the optimal regimen of a treatment of osteoporosis with an intravenous bisphosphonate one needs to know the duration of action of a single dose of the given drug. This allows us to establish the frequency by which a given dose has to be administered for obtaining a sufficient suppression of bone resorption over a longer period. In this study 1 and 2 mg Ibandronate were given as a single i.v. injection to young normal men and to healthy postmenopausal women on a free diet and with no treatment or supplements, and the markers of bone metabolism, as well as BMD, were followed for 6 months. Urinary C-telopeptides decreased by 81-95% 1 week after the injection and remained significantly decreased for 2 weeks after 1 mg Ibandronate, and for 4 months after 2 mg. In men, PTH increased by 80% at one week and remained significantly increased for 2 weeks, after 1mg and 2 mg Ibandronate. Plasma osteocalcin decreased slowly over 2 months in all 3 groups by 22%. Alkaline phosphatase showed similar, but not significant changes. In conclusion, the inhibition of bone resorption induced by 1 mg Ibandronate i.v. does not exceed 1 month and does not allow 3 month intervals in the treatment of osteoporosis, while 2 mg cover 3 months at least.

Keywords: Intravenous Bisphosphonate, Ibandronate, Normal Volunteers, Bone Metabolism

Introduction

Bisphosphonates are given intravenously in the treatment of malignant hypercalcemia and of Paget's disease, and for the prevention of skeletal related events in breast carcinoma and myeloma. Therapeutic efficacy has also been shown in osteoporosis, but the frequency at which a given dose has to be repeated for optimal efficacy is actually debated. High bone turnover is linked to higher fracture risk[1] and a lowering of bone resorption with improved bone density and decreased fracture incidence[2]. Even the early decrease of resorption markers after initiation of treatment is correlated with the later rise in BMD[3]. For these reasons, continuous suppression of bone resorption, as obtained with oral administration of bisphosphonates, is considered to be desirable. But after each drop in resorption markers that immediately follows intravenous administration, bone turnover tends to rise again until the next dose is given. The degree of the suppression and the duration of a single dose of bisphosphonates depend both on the dose of the given bisphosphonate and on the underlying disease[4,5]. For example, in malignant disease, monthly treatments are recommended, because bone turnover is accelerated, while in osteoporosis, 3 monthly administrations of three times smaller doses have been shown to increase BMD.

In order to know the optimal regimen for each bisphosphonate, the duration of the action on bone and calcium metabolism of a single dose has to be known, as well as its dose dependence. This will allow one to establish the frequency by which the given dose has to be administered for obtaining a more or less constant suppression of bone resorption, or which dose has to be given at a given frequency for obtaining the same effect. The effect of one single i.v. dose of Pamidronate in normal volunteers lasts for over 2 months[6]. For Ibandronate, it is known that 3 months after one intravenous dose of 1 mg or less in osteoporotics, resorption markers are back to the control values[7]. This study analyzes the effect of one i.v. administration of 1 or 2 mg Ibandronate monitored over 6 months on bone metabolism and BMD.

Subjects and methods

Twelve healthy young men, mean age 28 years (range 23

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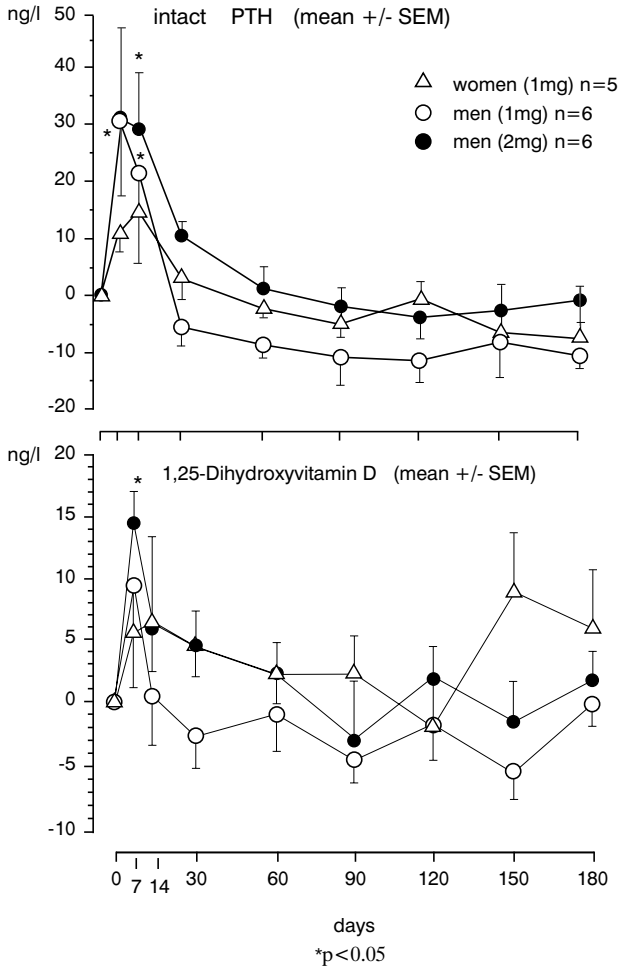

Figure 1. Percent changes (± SEM) of plasma PTH over 6 months and plasma 25 (OH)Vitamin D over 6 months after a single i.v. injection of 1 or 2 mg Ibandronate in healthy subjects.
* means significant difference from baseline by ANOVA analysis of variance.

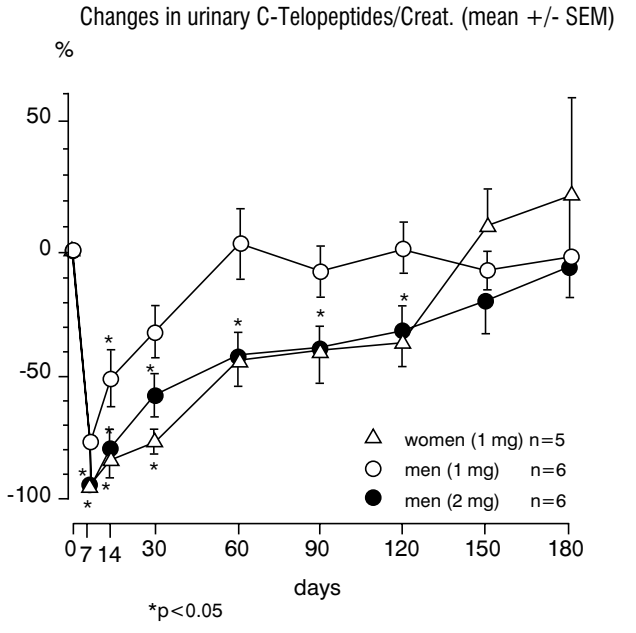

Figure 2. Percent changes (± SEM) of fasting urinary C-telopeptides / creatinin over 6 months after a single i.v. injection of 1 or 2 mg Ibandronate in healthy subjects.
* means significant difference from baseline by ANOVA analysis of variance.

to 43) and 5 postmenopausal women, mean age 60 years (range 53 to 65) were included. None had osteoporosis, when BMD was measured by DXA (Hologic QDR 2000, Waltham MA, USA). All had normal body mass index, normal renal function, and none was on medication. Fasting blood and two hour urinary samples were taken in the fasting state one week before the test, for assuring normal baseline values in all volunteers, and again just before injection of the drug. The latter values were taken as baseline for calculation of the changes induced by the drug.

Six men and 5 women received 1 mg Ibandronate i.v. as a bolus injection given in the morning and in the fasting state. Six men received a 2 mg Ibandronate under the same conditions. Urinary and blood tests were then repeated at day 7, 14, 30, 60, 90, 120, 150 and 180. BMD measurements were repeated at day 90 and 180. During this time, nutritional intake was free, and no calcium or vitamin D supplements were given.

Plasma PTH was measured with an IRMA assay (Intact PTH chemiluminescence assay, Nichols Institute, San Juan Capistrano, CA, USA), Osteocalcin with an IRMA (Elsa-Osteo, Cis bio int, 6if sur Yvette, France) 1,25-dihydroxyvitamin D with RIA (Diasorin, Stillwater, MI, USA), urinary C-telopeptides with ELISA CrossLaps (Osteometer Biotech, Denmark). Plasma calcium, alkaline phosphatase, urinary calcium and creatinine were measured by routine laboratory methods.

Bone densitometry was performed by DXA (Hologic 2000) in all subjects before the administration of Ibandronate, and again 3 and 6 months later. The results on lumbar spine and femoral neck are reported. The Hologic 2000 densitometer has a precision of 1% for lumbar BMD, and 1.5% for hip BMD *in vivo* in normal subjects in our institution.

Baseline values were compared between groups by analysis of variance. Biochemical values and BMD results after the treatment were evaluated by one way analysis ANOVA.

Results

Basal characteristics and biochemical data are given in Table 1. Although the mean age of the groups was different, there were no significant differences in baseline values of bone turnover, except for the lower levels of osteocalcin in the postmenopausal women. The mean BMD was higher in the men receiving 1 mg, than in the other groups, which were partially osteopenic.

	Men - 1 mg Ibandronate	Men - 2 mg Ibandronate	Women - 1 mg Ibandronate
Number	6	6	5
Age (years)	21.5 (± 0.6)	31.2 (± 3.4) *	59.0 (± 1.9) */**
Plasma Calcium (mmol/l)	2.21 (± 0.03)	2.23 (± 0.02)	2.27 (± 0.05)
Plasma Creatinine (mmol/l)	93.8 (± 4.2)	93.0 (± 2.4)	93.0 (± 3.9)
Plasma PTH (ng/l)	40.0 (± 5.6)	37.5 (± 4.3)	43.8 (± 5.6)
1,25(OH)2 Vit. D (ng/ml)	35.2 (± 3.8)	28.7 (± 1.9)	25.9 (± 6.1)
Plasma Osteocalcin (mg/l)	33.2 (± 1.6)	27.2 (± 2.6)	15.5 (± 2.0)*/**
Alkaline Phosphatase(IU/l)	63.0 (± 6.3)	67.2 (+ 7.8)	72.6 (± 11.5)
Ur. Calcium (mol/mol creat)	0.198 (± 0.052)	0.200 (± 0.046)	0.112 (± 0.026)
Ur. C-telopeptides (mg/mmol creat.)	314 (± 50)	353 (± 63)	191 (± 34)
BMD L2-L4 (g/cm^2)	1.043 (± 0.035)	0.914(± 0.045)Γ	0.875 (± 0.070)Γ
(T score)	-0.66 (± 0.32)	-1.83 (± 0.41)	-1.86 (± 0.64)
BMD femoral neck (g/cm^2)	0.980 (± 0.034)	0.802 (± 0.050)*	0.752 (± 0.071)*
(T score)	0.01 (± 0.31)	-1.57 (± 0.47)*	-1.42 (± 0.71)*

Γ $p = 0.05$ compared with men - 1mg, * $p < 0.05$ compared with men - 1 mg.

** $p < 0.05$ compared with men - 2 mg.

Table 1. Baseline characteristics (mean ± SEM).

The effects of Ibandronate on the biochemical markers over 6 months are shown on the graphs. The number of subjects being relatively small, and the groups not strictly homogenous, any comparison between groups deserves some caution. But the duration of the metabolic response can be appreciated within each group, and concerning their bone metabolism the postmenopausal women included in this trial can be considered as close, although not identical, to patients with postmenopausal osteoporosis .

Plasma calcium corrected for albumin, dropped in the average by - 4.1% in the men, within the normal range, but not in the women. In the men, the decrease remained significant for 2 weeks. The effect on plasma PTH and $1,25(OH)_2$ Vitamin D is shown in Figure 1. Plasma PTH increased in men by about 80% at one week, and remained significantly increased for 2 weeks after 1 mg and 2 mg Ibandronate. In the women, the rise of PTH was small and not significant. Serum $1,25(OH)_2$ Vitamin D increased in parallel with the PTH levels. In the men, the increase was significant only at 1 week, and the levels were back to baseline very soon, 2 weeks after 1 mg Ibandronate and 2 months after 1 mg. In the women, the increase was not significant.

The effect on urinary C-telopeptides is shown in Figure 2. Urinary C-telopeptides decreased in men by 81% one week after 1 mg Ibandronate, and by 95% after 2 mg. The decrease remained significant for 2 weeks after 1 mg Ibandronate, and for 4 months after 2 mg. In the women, urinary C-telopeptides decreased by 95% after 1 mg Ibandronate and remained significantly lowered for 1 month. In men the differences between the doses were also valid when absolute values were considered (not shown).

Urinary calcium creatinine ratio dropped significantly after 1 mg Ibandronate for 1 week, and then increased again slowly over 2 to 3 months.

The effect on osteocalcin and alkaline phosphatase is shown in Figure 3. Plasma osteocalcin decreased slowly over 2 months in all three groups by 22%, and remained decreased for 5 to 6 months (significantly only after 1 mg). Alkaline phosphatase did not change significantly. It decreased slightly, in men with a nadir of about -20%, 2 to 3 months after the injection of Ibandronate. In women it first increased by 10%, and then dropped slightly to -12% at 3 months.

BMD of the lumbar spine (L2-L4) increased in all subjects (except in one woman), especially during the first 3 months following the administration of the drug. After that it dropped again in most of the subjects (13/17). The mean increase after 3 months was +2.01% after 1 mg Ibandronate, +3.20% after 2 mg in the men, and +2.18 in the women. The increase after 6 months was +1.26% for 1 mg, +2.44% for 2

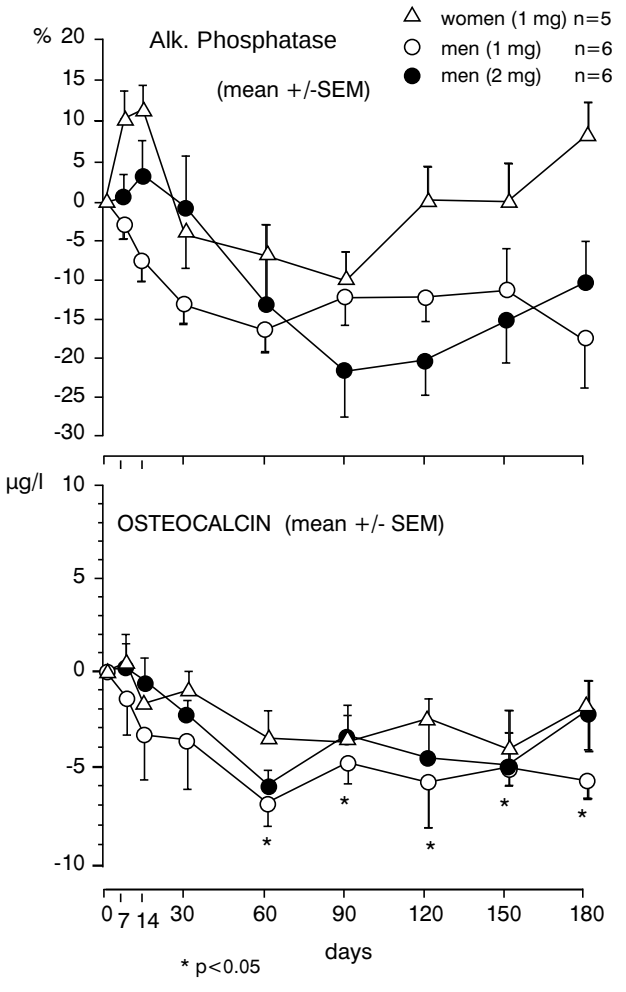

Figure 3. Percent changes (± SEM) of plasma alkaline phosphatase and plasma osteocalcin over 6 months after a single i.v. injection of 1 or 2 mg Ibandronate in healthy subjects.
* means significant difference from baseline by ANOVA analysis of variance.

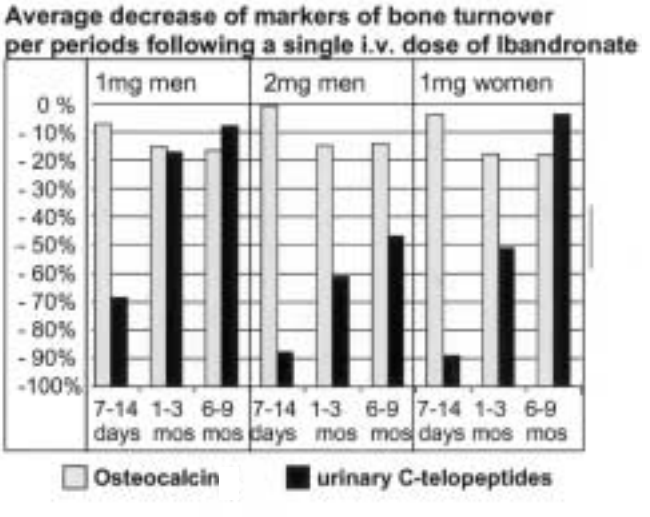

Figure 4. Mean % decreases of plasma osteocalcin and urinary C-telopeptides per periods after a single i.v. injection of 1 or 2 mg Ibandronate in healthy subjects.

mg in men, and +1.64% for 1 mg in women. BMD of the femoral neck increased by +1.06% in the men with 1 mg Ibandronate. These changes in BMD were significant only in paired T-test and in the men, because one woman showed a drop in lumbar BMD during the first 3 months.

Discussion

The extent and the duration of the anti-resorptive effect of one single injection of Ibandronate were both dose-dependent, as already shown in osteoporotic patients[7]. Since in this study no further injections were given, the duration of the effect on bone metabolism could be examined almost until its end. The anti-resorptive effect in the men lasted for less than 2 months after the administration of 1 mg Ibandronate, and more than 2 months after 2 mg Ibandronate. This is in agreement with the effects reported with intravenous Pamidronate, Alendronate, and Ibandronate, unless the drugs were tested in diseases with accelerated bone turnover, such as primary hyperparathyroidism and malignant hypercalcemia (see Table 2)[5,6,8-10]. It can be assumed from this literature that patients with osteoporosis show similar responses to intravenous bisphosphonates as normal subjects. The difference observed here between the relatively young men and the postmenopausal women, with the women depressing bone resorption longer than the men who got the same dose of 1 mg might be explained by the lower bone turnover of the latter, as judged by the significantly lower initial levels of osteocalcin, and the lower urinary excretion of telopeptides and calcium (n.s.). That bone turnover is higher in young men than in postmenopausal women has to be stressed here as a physiological phenomenon, and has not to be confounded with the difference between postmenopausal and premenopausal women. The difference in age between the two groups of men was too small for causing any differences in bone turnover. There was, however, a difference in BMD, but it has not been reported that this influences the biochemical response to bisphosphonates.

In general, the decrease of markers of bone formation was slow and dose-dependent. The return back to the initial values indicates the very end of the metabolic effect of the drug. Although osteocalcin remained slightly depressed over 6 months in all groups, alkaline phosphatase reincreased already after 2 to 3 months.

The early effect on BMD was short, since BMD declined again after the first 3 months in most cases, which is not surprising after one single dose. Indeed, this can be explained by the observation made with 1 mg Ibandronate, that after 3 months bone resorption rises again while bone formation is still depressed. But it is still possible that a higher single dose

Drug	Subjects, Disease	% change of marker	Time of max. Effect	Time of Recovery	Reference
Bone resorption: Urinary Hydroxyproline/Creatinine					
Pamidronate 30 mg	Malignant Hypercalcemia	- 50 %	6 days	>2 weeks	2
Pamidronate 20 mg	Young normal men	- 55 %	3 days	>2 months	4
Pamidronate 30 mg	Osteoporosis	- 33 %	<3 months	? (repeated dose)	1
Alendronate 5 mg	Primary Hyperparathyroidism	ca. - 45 %	1 week	1 month	3
Alendronate 5 mg	Osteopenia	ca. - 55 %	2 weeks	2 month	3
Alendronate 10 mg	Osteoporosis	ca. - 25 %	≤3 months	? (repeated dose)	6
Alendronate 30 mg	Osteoporosis	ca. - 45 %	≤1 month	>6 months	7
Alendronate 30 mg	Osteoporosis	- 40 %	1 week	>2 years	5
Bone resorption: urinary C-terminal telopeptides					
Ibandronate 1 mg	Osteoporosis	ca. - 55 %	≤1 month	>3months? (repeat.dose)	9
Ibandronate 2 mg	Osteoporosis	ca. - 65 %	≤1 month	3 months	9
Bone formation: alkaline phosphatase					
Pamidronate 20 mg	Normal men	- 9 %	2 months	>2 months	4
Pamidronate 30 mg	Osteoporosis	ca. - 12 %	<3 months	? (repeated dose)	1
Alendronate 5 mg	Primary Hyperparathyroidism	ca. - 15 %	4 weeks	>2 months	3
Alendronate 5 mg	Osteopenia	ca. - 15 %	2 weeks	6 weeks	3
Alendronate 10 mg	Osteoporosis	ca. - 9 %	≤3 months	? (repeated dose)	6
Alendronate 30 mg	Osteoporosis	ca. - 15 %	6 months	>6 months	7
Alendronate 30 mg	Osteoporosis	- 23 %	3 months	2 years	5

Comments: In high bone turnover (malignant hypercalcemia and primary hyperparathyroidism), the effect is more pronounced and shorter than in normals subjects and osteoporotics. In the latter, the effect lasts partially for 6 and more months.

Table 2. Comparison of maximal effects on markers of bone metabolism of various bisphosphonates given intravenously.

prevents at least bone loss, as shown in postmenopausal women[11].

These observations allow the conclusion that 1 mg Ibandronate given intravenously for the treatment of osteoporosis does not inhibit bone resorption sufficiently for allowing 3 monthly intervals, while the metabolic effect of 2 mg seems to cover 3 months at least. This also explains why Pamidronate given at three monthly intervals increased BMD by a degree comparable to that obtained by continuous oral administration of bisphosphonate[3,7], and why 2 mg Ibandronate injected every 3 months could sharply increase BMD in men with hypogonadal osteoporosis[12]. Whether higher doses of Ibandronate exert longer effects allowing more time between injections, remains open.

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