

Effects of cyclic therapy with intranasal carbocalcitonin in healthy spontaneous postmenopausal women

D. DE ALOYSIO - F. PANSINI (*) - C. CAMPOBASSO (*) - L. ZANOTTI (*)
A. D. ABBRUZZESE (*) - M. MAULONI - F. BOTTIGLIONI

Summary: Carbocalcitonin spray administered for 12 months at a daily dosage of 80 U MRC according to five schedules has been tested on 150 normal spontaneous postmenopausal women for its influence on bone mineral density (BMD), bone metabolism and osteoarticular pain. BMD was monitored before and at the end of treatment in comparison with BMD of untreated control women. Metabolic markers (serum alkaline phosphatase, serum osteocalcin and urinary hydroxyproline) were also evaluated before and during treatment (at the 9th or 10th month of treatment). Osteoarticular pain was assessed by an analogic visual scale. Intranasal carbocalcitonin, administered according to cyclic schedules at a high frequency dosage, was able to maintain bone mass only in the earlier postmenopausal women. BMD percent increase after 12 months of treatment was 1.10 and 1.31 in women with low (<0.870 mg/cm²) and high baseline BMD (≥ 0.870 mg/cm²), respectively. In advanced menopause the maintaining effect of carbocalcitonin on BMD seemed evident only if the baseline bone mass was lower than the BMD of the age matched control group. At least six months of treatment/year is necessary for effective therapy. Both systemic and local tolerance were optimal. No significant side-effects were detected.

Key words: Osteoporosis; Spontaneous menopause; Spray carbocalcitonin.

INTRODUCTION

Osteoporosis is an increasing and major public health problem as our population ages. It is characterized by decreased bone mass and increased susceptibility to

fractures. Postmenopausal bone loss and subsequent osteoporosis are consequences of a change in bone metabolism with an increased resorption process leading to negative bone turn-over.

Osteoporosis is more common in women than men as the consequence of the accelerated bone loss occurs during menopause after cessation of ovarian function^(1, 2). Advances in the prevention of osteoporosis has been facilitated by the advent of accurate and precise methods of bone density measurement⁽³⁾.

The target of postmenopausal osteoporosis prevention is maintaining bone mass by inhibiting the absorption of bone mi-

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Departments of Obstetrics & Gynecology
University of Bologna, Italy
(*) University of Ferrara, Italy

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neral content or implementing osteosynthesis. Pharmacological development in prevention of osteoporosis includes a lot of drugs: estrogens, vitamin D, calcium, calcitonin, biphosphonates and anabolic steroids. Each of them has been widely assessed in comparison for the advantages and side-effects, length of therapy, dosage and route of administration. Calcitonin, together with estrogens, has been approved by the FDA as treatment of established osteoporosis in the US⁽⁴⁾.

Calcitonin, identified in 1962, is a peptide of 32 aminoacids of about 3500 mol wt, and is characterized by its ability to inhibit bone resorption⁽⁵⁾. This drug can be administered intramuscularly, intravenously, subcutaneously and by nasal spray route. Salmonated form has been the most common calcitonin used successfully in long-term management of postmenopausal osteoporosis⁽⁶⁾.

Intramuscular administration of salmon calcitonin for many years was the only administration route. However, this route proved to have a low compliance especially in long-term therapies. For this reason the nasal administration route has been more commonly used, having an obviously higher compliance than the intramuscular route. Nasal mucosa allows for sufficient absorption of the hormone resulting in plasma levels of the hormone comparable to the ones obtained by intramuscular administration. Many studies have compared the efficiency of both parenteral and spray routes of salmon calcitonin in maintaining bone mass⁽⁷⁾. A medical advisory panel of the US-FDA voted for the registration of nasal calcitonin for treatment of osteoporosis in November 1994. Intranasal administration provides about half the effect of the injectable form of calcitonin⁽⁸⁾. To have an effect on bones in early postmenopausal women, 400 IU of injectable calcitonin may have to be used, and the intranasal form might require a higher dose of the hormone. However, clinical trials of

intranasal calcitonin showed efficacy at low doses (50 IU)⁽⁷⁾.

A new form of calcitonin (carbocalcitonin/Eel calcitonin), characterized by higher molecular stability compared with other calcitonins, was synthesized in 1977⁽⁹⁻¹¹⁾. However, data on the efficacy of this calcitonin in maintaining bone mass density are still in contrast, while results of the effects on osteoarticular pain are in agreement^(12, 13). Recent evidence indicates that a combined regimen of carbocalcitonin and estrogens increases vertebral bone mass in early postmenopausal women much more than carbocalcitonin or estrogens alone⁽¹⁴⁾.

The aim of this study was to investigate by a controlled trial in a sample of healthy women the effects of spray carbocalcitonin administered by cyclic schedule on bone mass, bone metabolism and osteo-articular pain.

SUBJECTS AND METHODS

Patient recruitment and treatment schedules

One hundred and fifty patients aged 54.5 ± 3.6 years (mean \pm SD) were recruited at the Center of Physiopathology of Climacteric and Postmenopause, University of Bologna from January 1990 to May 1992. They were enrolled into twelve month trial to evaluate the effects of intranasally following inclusion criteria: (i) smoking less than 10 cigarettes/day; (ii) no abuse of alcohol (< 500 cc of wine/die); (iii) absence of secondary amenorrhea longer than 12 months; (iv) normal BMI (25.6 ± 4.0 , mean \pm SD); (v) absence of past or present history of pathologies interfering with phosphorus and calcium metabolism (dysthyroidism, diabetes, rickets, osteomalacia, chronic hepatic pathology, chronic renal, failure immobilizing neuropathology, malaabsorption, neoplasms); (vi) use of oral contraceptives for less than 24 months; (vii) never use of HRT or any drugs interfering with calcium metabolism.

Seven per cent of the women were nullipara, 35% primipara, 58% multipara. Mean patient age was 52 ± 31 years. Mean body mass index (BMI) was 25.4 ± 3.4 . Forty-five per cent of patients exercised regularly, while 55% of them had a sedentary life style. Osteoarticular pain was absent in 13% of the subjects while in 74% it was present but mild, and severe in 13% of cases.

The patients thus recruited were divided into two groups according to time since menopause. The first (early postmenopause) included 75 patients with last menses from 6 to 24 months. The second (late postmenopause) included 75 patients with elapsed time from last menses 25 to 120 months. The patients of each group were divided into 5 subsets (each of them with 15 subjects) according to therapeutic schedules. Intranasal carbocalcitonin was administered with a daily evening dosage of 80 U MRC according to five therapeutic schedules: (i) one month of daily cyclic treatment with three months free interval (subset 1); (ii) two months of daily cyclic treatment with two months free interval (subset 2); (iii) one month of daily cyclic treatment with one month free interval (subset 3); (iv) two months of daily cyclic treatment with one month free interval (subset 4); (v) three months of treatment with one month free interval (subset 5). Subsets 1 and 2 were considered as "low frequency administration" while subsets 3, 4 and 5 as "high frequency administration".

Bone mass density (BMD) was measured before treatment (T0) and after one year of therapy (T12). BMD average at time T0 was 0.829 ± 0.098 (mean \pm SD, g/cm²). The women were divided into two subgroups according to T0-BMD ("high" and "low" BMD). BMD subgroups were defined as "early" or "late" postmenopause, according to BMD values, 0.870 and 0.776 (g/cm²), chosen threshold, respectively.

Bone mass density (BMD) was measured at the lumbar spine (L2-L4) with double photon absorptiometry (Norland, mod. N2601 Ax3).

Before beginning therapy a dietetic caloric plan (± 1490 Kcal/day) and total body physical training (20 minutes/day) were prescribed. Patients were also invited to fill in an analogic visual scale for pain during treatment (0 = absence of pain, 100 = unbearable pain).

Biochemical tests

Fasting serum alkaline phosphatase (sAP) was measured enzymatically and plasma bone Gla protein (also called osteocalcin, BGP) was measured by enzymatic and radioimmunological assays, respectively. Fasting urinary total hydroxyproline/creatinine (uHpr/Cr) was assessed by a spectrophotometric method. All parameters were measured at 8.00 AM, before and during treatment: during the 9th month of the trial for subset 1 (at the third therapeutic cycle), for subset 3 (at the fifth therapeutic cycle) and for subset 5 (at the third therapeutic cycle). The parameters in subsets 2 and 4 (both at the fourth therapeutic cycle) were measured during the 10th month of treatment.

Drop out

Sixteen women did not complete the trial, corresponding to 10.6% of the whole sample. Effective days of treatment with, daily dosage of 80 U MRC intranasal carbocalcitonin (as reported by the patients in note books given to each of them) was 103 ± 29 (means \pm SD) for subsets 1 and 2, considered together, and 231 ± 51 for subsets 3, 4, 5 considered together.

Drop-outs were: 11.6% (7/60) and 10% (9/90) for the treatment groups with lower and higher dosages, respectively.

Reasons for drop-out were not reported in 5.3% of the cases (8/150). In 3.3% of the cases (5/150) the reasons for drop-out were diseases not related to carbocalcitonin therapy. Of these, two cases were related to car accidents and three cases to respiratory complications. In 2% of the cases (3/150) the reasons were side effects from carbocalcitonin (two cases for complaints of local nose irritation and one case for nausea).

Control groups

Seven hundred and fifty apparently normal women recruited in the same Menopausal Center were considered as controls. All women had a BMI in the normal range (25.4 ± 4.0 , mean \pm SD) and none received HRT or other therapies. From these women two control groups were selected. The first one included all the 750 women. This group was used to calculate BMD reference values according to menopausal status and age and included 211 premenopausal and 539 spontaneous postmenopausal women (time elapsed since last menses: 6-12 months). The second group included 48 randomly selected subjects for comparison of biochemical tests and the visual analogic pain scale. This group was divided into two subgroups according to months since menopause: 16 women (1st subgroup) with 6-24 months and 32 women (2nd subgroup) with 25-120 months elapsing since last menses.

Statistical analysis

Differences between sample means of data were evaluated using analysis of variance (Anova) at the Interuniversity Center for North-East Italy, Casalecchio di Reno, Bo (CINECA).

Ethical warnings

The study was done in accordance with the ethical warnings of the Helsinki declaration (1964), elaborated at the Tokyo Conference (1975) and at the World Medical Assembly in Venice (1983).

Table 1. – *Effect of 12 months spray carbocalcitonin on bone density (BMD) according to time menopause and dosage frequency.*

	Early menopause			Late menopause		
	Dosage frequency		p	Dosage frequency		p
	LoW	High		Low	High	
T0-BMD	0.871±0.081	0.865±0.075	NS	0.807±0.123	0.796±0.108	NS
T12-BMD	0.836±0.085	0.875±0.079	<0.05	0.798±0.123	0.787±0.102	NS
Δ %	–4.02	+1.16		–1.12	–1.13	

T0- and T12-BMD denote bone mass density measured at baseline and after 12 months of treatment, respectively. Absolute values are expressed as mean ± SD; p indicates probability level for difference by Anova; NS: not significant.

RESULTS

Effect on bone mass density

Carbocalcitonin appears to maintain bone mass after 12 months of treatment only in early menopausal women if used according to high frequency schedules (Table 1). BMD change detected in these patients was +1.16%. BMD percent changes in early menopausal women using low dosage frequency schedules, in late menopausal women using low and high dosage frequency schedules were –4.02, –1.12 and –1.13, respectively. BMD at baseline does not appear to influence BMD changes after therapy in the early menopausal women, using both low and high frequency dosage schedules (Table 2). A positive maintaining effect on bone mass emerges in late menopause in wo-

men using carbocalcitonin with high dosage frequency only if baseline BMD was less than the cut-off value separating low and high BMD groups (Table 3). In these patients the BMD percent change after therapy was of +1.32.

Effect on bone metabolism

Spray carbocalcitonin administered to the spontaneous postmenopausal group induced significant decrease in bone metabolic markers both in early and late menopausal women after 12 months of treatment (Table 4).

Baseline serum levels of biochemical markers of bone formation (serum alkaline phosphatase and osteocalcin) and bone resorption (urine hydroxyproline/creatinine) among subjects undergoing treatment

Table 2. – *Effect of 12 months spray carbocalcitonin in early menopause on bone mass density (BMD) according to dosage frequency and BMD.*

	Dosage frequency					
	Low			High		
	Low-BMD	High BMD	p	Low BMD	High BMD	p
T0-BMD	0.860±0.031	0.882±0.023	<0.05	0.818±0.067	0.918±0.042	<0.05
T12-BMD	0.826±0.023	0.845±0.019	<0.05	0.827±0.049	0.930±0.071	<0.05
Δ%	–3.95	–4.20		+1.10	+1.31	

T0- and T12-BMD denote bone mass density measured at baseline and after 12 months of treatment, respectively. Absolute values are expressed as mean ± SD (mg/cm²). BMD value of 0.870 mg/cm² (median value of population) was chosen as cut-off to separate low- and high-BMD groups; p indicates probability level for difference by Anova; NS: not significant.

Table 3. – Effect of 12 months spray carbocalcitonin in late menopause on bone mass density (BMD) according to dosage frequency and BMD.

	Dosage frequency					
	Low			High		
	Low-BMD	High BMD	p	Low BMD	High BMD	p
T0-BMD	0.692±0.062	0.884±0.085	<0.05	0.682±0.068	0.838±0.063	<0.05
T12-BMD	0.686±0.108	0.870±0.080	<0.05	0.691±0.077	0.822±0.075	<0.05
Δ%	–0.87	–1.58		+1.32	–1.91	

T0- and T12-BMD denote bone mass density measured at baseline and after 12 months of treatment, respectively. Absolute values are expressed as mean ± SD (mg/cm²). BMD value of 0.776 mg/cm² (median value of population) was chosen as cut-off to separate low- and high-BMD groups; p indicates probability level for difference by Anova; NS: not significant.

and control ones, matched for time since menopause, did not show any significant difference. Percentage changes of resorption markers were higher than the ones of bone formation. Total hydroxyproline/creatinine decreased by 21.05% and 22.67% in early and late menopause, respectively. Serum alkaline phosphatase and osteocalcin decreased by 17.06% and 16.01% in early menopause, and by 19.11% and 18.77% in late menopause respectively.

Effects on articular pain

The visual analogue pain score scale did not show any significant variations of

intensity with age or administration of carbocalcitonin. On the contrary, a significant reduction of articular pain was observed both an absolute and percentage values. The effect was related positively with dosage of carbocalcitonin.

Side effects

Nausea and local irritation in the nose were found in 21 of 50 women (42%). Of the 134 patients recruited who did not drop out of the study, only one complained of irritation in the nose and one complained of flushing. Overall, tolerance to the drug was good and no significant troublesome side effects were observed.

Table 4. – Longitudinal evaluation of bone metabolic markers in absence of treatment (control) and after treatment with spray carbocalcitonin in early and late spontaneous postmenopausal women.

		Early menopause			Late menopause		
		Baseline	At the 10th month	p	Baseline	At the 10th month	p
sAP	treated	117.9±18.2	97.2±16.7	<0.05	119.3±15.2	96.5±13.2	<0.05
	control	115.6±13.5	114.3±14.4	NS	116.1±16.1	118.2±14.9	NS
BGP	treated	8.42±1.92	6.23±1.04	<0.05	8.69±2.13	6.19±1.08	<0.05
	control	8.53±2.01	8.70±2.05	NS	8.64±2.08	8.78±2.12	NS
OH-pr/Cr	treated	0.076±0.019	0.060±0.014	<0.05	0.075±0.014	0.058±0.012	<0.05
	control	0.074±0.016	0.077±0.018	NS	0.073±0.017	0.078±0.015	NS

Absolute values are expressed as mean ± SD. sAP: serum alkaline phosphatase; BGP: osteocalcin; OH-pr/Cr: urinary hydroxyproline/creatinine; p indicates probability level for difference by Anova; NS: not significant.

CONCLUSIONS

The literature on the effect of carbocalcitonin on bone mass and metabolism is contradictory^(9, 11, 14). Studies on the efficacy of carbocalcitonin have been conducted without considering time since menopause and cyclic administration schedules. It is well known that bone mass is mostly lost during the first 3-4 years after menopause. After this period, bone mass decrement settles on a constant rate of about 1%. For this reason evaluation of the efficacy of osteo-protective therapy on maintaining bone mass should be done within this time lapse. Moreover, continuous calcitonin therapy is not thought to be so effective because of either receptor down-regulation or antibody formation, especially from sources such as salmon calcitonin⁽¹⁵⁾. In fact, in cases of steady state levels of the hormone, the osteoclastic receptor is less active.

Our results demonstrated that spray carbocalcitonin, administered according to high frequency cyclic schedules, is able to inhibit bone loss. This effect was evident in the early postmenopausal women compared to untreated controls. However, in advanced menopause this effect seems evident only if the baseline bone mass was below the normal age-matched range. The effect of carbocalcitonin on bone mass agrees with the observed biochemical metabolic changes. Moreover, we confirmed that spray carbocalcitonin was effective in the relief of osteoarticular pain^(12, 13). Systemic and local compliance were excellent and the side-effects were not significant. The long-term efficacy of the administration of spray carbocalcitonin in maintaining bone mass and preventing fractures remains to be demonstrated.

In conclusion, the use of carbocalcitonin may be proposed as an alternative in the preventive treatment of postmenopausal osteoporosis.

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Address reprint requests to:

F. PANSINI
Via Argine Ducale, 166
44100 Ferrara (Italy)