

Is addition of sodium fluoride to cyclical etidronate beneficial in the treatment of corticosteroid induced osteoporosis?

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Abstract

Objective—To investigate whether administration of sodium fluoride (NaF) in addition to cyclical etidronate has a positive effect on bone mineral density (BMD) in patients with established osteoporosis during continued treatment with corticosteroids.

Patients and methods—47 patients who were receiving treatment with corticosteroids were included in a two year randomised, double blind, placebo controlled trial. Established osteoporosis was defined as a history of a peripheral fracture or a vertebral deformity, or both, on a radiograph. All patients were treated with cyclical etidronate, calcium, and either NaF (25 twice daily) or placebo. Vitamin D was supplemented in the case of a low serum 25 (OH) vitamin D concentration. BMD of the lumbar spine and hips was measured at baseline and at 6, 12, 18, and 24 months.

Results—After two years of treatment, the BMD of the lumbar spine in the etidronate/NaF group had increased by +9.3% (95% confidence intervals (CI): +2.3% to +16.2%, $p < 0.01$), while the BMD in the etidronate/placebo group was unchanged: +0.3% (95% CI: -2.2% to +2.8%). The difference in the change in BMD between groups was +8.9% (95% CI: +1.9% to +16.0%, $p < 0.01$). For the hips, no significant changes in BMD were observed in the etidronate/NaF group after two years: -2.5% (95% CI: -6.8% to +1.8%); in the etidronate/placebo group BMD had significantly decreased: -4.0% (95% CI: -6.6% to -1.4%; $p < 0.01$). The difference between the groups was not significant: +1.5% (95% CI: -3.4% to +6.4%). No significant differences in number of vertebral deformities and peripheral fractures were observed between the two groups.

Conclusion—The effect of combination treatment with NaF and etidronate on the BMD of the lumbar spine in corticosteroid treated patients with established osteoporosis is superior to that of etidronate alone.

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It is well known that corticosteroids have a negative effect on bone,¹⁻³ which may lead to

bone loss^{4,6} and, ultimately, fractures.⁶⁻⁸ Patients with osteoporosis, demonstrated on radiographs by vertebral deformities, have an increased risk of further fractures.⁹ Thus, corticosteroid treated patients with established osteoporosis are at high risk for further fractures, and prevention of further osteoporosis is clinically relevant in these patients.

As yet, randomised, double blind, placebo controlled studies on the effect of drugs to prevent or treat osteoporosis in patients who use corticosteroids are scarce. As inhibition of bone formation is an important factor in the pathogenesis of corticosteroid induced osteoporosis¹⁻³ and as sodium fluoride (NaF) has a positive effect on bone formation,¹⁰⁻¹² NaF, at least theoretically, could be a promising treatment for corticosteroid induced osteoporosis. Positive effects of NaF on vertebral bone mineral density (BMD) in corticosteroid treated patients have been described in retrospective, open prospective, and non-randomised studies.¹³⁻¹⁵

We performed a randomised, double blind, placebo controlled trial to determine whether NaF (25 mg twice daily) has an additive effect to treatment with cyclical etidronate on the BMD of the lumbar spine and hips in corticosteroid treated patients with established osteoporosis. All patients received cyclical etidronate, because positive effects of cyclical etidronate on BMD have been described for corticosteroid treated patients.¹⁶⁻¹⁸

Methods

PATIENTS

Forty seven patients were enrolled in a randomised, double blind, placebo controlled study between July 1991 and September 1993. Patients were recruited from de Wever (Heerlen), Maasland (Sittard), and St Antonius (Nieuwegein) Hospitals and University Hospital Utrecht. Approval of the medical ethics committee of each hospital was obtained, and all patients gave their informed consent.

Patients from the Departments of Rheumatology and Clinical Immunology, Nephrology, and Pulmonology were included. The patients had rheumatoid arthritis (n=23), systemic lupus erythematosus (n=10), other connective tissue disorders (n=8), chronic obstructive pulmonary disorder (n=3) or polymyalgia rheumatica (n=2); in one patient corticosteroids were prescribed because of a heart transplantation.

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All patients used at least 7.5 mg prednisone daily at the start of the study, and it was expected that it would be necessary to continue this medication for at least six months. The dose of corticosteroids, determined by the treating physician, was not related to the study protocol.

All patients had established osteoporosis, defined by a vertebral deformity on a radiograph or a previous peripheral fracture, or both. Nowadays, patients are usually selected for a clinical trial on the basis of the BMD. However, this trial was started in 1991. At that time, it was customary to enroll patients in a clinical trial for osteoporosis because they had osteoporotic fractures.

All patients received a supplement of at least 500 mg elementary calcium/day (Calcium Sandoz Forte). Patients with a low daily calcium intake (< 500 mg/day), assessed by means of a short questionnaire on dietary calcium intake, were given 1000 mg elementary calcium/day. Vitamin D (0.2 mg dihydroxycholesterol, half a tablet on alternating days) was prescribed if the serum 25 hydroxyvitamin D concentration was below the lower limit of normal (10 µg/l in winter and 15 µg/l in summer). Cyclical etidronate was prescribed for all patients: two weeks of treatment (200 mg twice daily) followed by 11 weeks without treatment (thus eight cycles of treatment in two years). Cyclical etidronate was taken between breakfast and lunch (10 00 am) and in the evening (10 00 pm).

Patients were randomly assigned to one of the two treatment groups. The randomisation was done in blocks per centre (each block consisted of eight patients: four for NaF and four for placebo). Patients were allocated to receive either an oral dose of 50 mg NaF/daily (Procal) or placebo. NaF (Procal) and placebo tablets were kindly supplied by Christiansen, the Netherlands. NaF was given as enteric coated tablets of 25 mg. The NaF (or placebo) had to be taken twice daily, between breakfast and lunch (10 00 am) and in the evening (10 00 pm). Calcium (and vitamin D, if necessary) was taken with or shortly after the evening meal.

BONE MASS MEASUREMENT

The bone mineral content (BMC) of the lumbar spine (L2-L4) and femoral neck was determined by dual energy x ray absorptiometry (Hologic QDR 1000, USA). The vertebral column was scanned at the level of L2-L4. The hips were scanned at the femoral neck. The BMD (g/cm²) was obtained by dividing the bone mineral content of each region by the projected bone area. The BMD of the hips was given as the mean of the values for the right and left hip. The precision, expressed as a coefficient of variation of duplicate measurements, was 1% for the lumbar spine and 1% for the femoral neck. Bone mass was measured at baseline and at 6, 12, 18, and 24 months.

FRACTURES

Radiographs of the thoracic (Th4 to Th12) and lumbar (L1 to L5) spine were obtained at

baseline and at 12 and 24 months. At baseline a vertebral deformity was defined as a loss of height of 15% or more of a vertebra (anterior, middle, posterior).¹⁹ A vertebral deformity on the radiographs taken one and two years after baseline was scored if there was a decrease in vertebral height (anterior, middle or posterior) of 15% in comparison to the height at baseline. Peripheral fractures were scored if visualised on a radiograph. Clinical vertebral fractures were scored if there was a vertebral deformity which caused clinical manifestations, leading to the prescription of therapy: bed rest or analgesics, or both.

LABORATORY TESTS

Blood and urine samples were collected at baseline and at 3, 6, 12, 18, and 24 months from all patients. Serum creatinine, calcium, phosphorus, alkaline phosphatase (AP), erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) and urinary excretion of creatinine, calcium, and hydroxyproline were determined for all patients on the same day that the samples were taken. The methods of determination were described earlier.²⁰

In a randomly selected group of 30 of the 47 patients we also measured serum osteocalcin (OC), bone alkaline phosphatase (BAP), carboxyterminal propeptide of type I procollagen (PICP), carboxyterminal cross linked telopeptide of type I collagen (ICTP), and urinary excretion of pyridinoline (Pyr) and deoxypyridinoline (Dpyr). These samples were also taken at baseline and at 3, 6, 12, 18 and 24 months. To minimise interassay variation, we measured these parameters after completing the study in one run. Samples were divided for the different determinations and frozen at -20°C until assay. All measurements were performed twice. Total OC was determined using a new human specific immunoradiometric assay (ELSA-OSTEO; Cis Biointernational, Bagnols, France), which recognises a large N-terminal mid-fragment in addition to the intact molecule.²¹ Normal values for postmenopausal women are 12.9-55.9 ng/ml, according to the manufacturer. Intra-assay and interassay coefficients of variation are 3.1% and 1.8%, respectively. BAP was determined with ELISA (Alkphase-B, Metra). Normal values for postmenopausal women are 14-43 U/l, according to the manufacturer. Measurement of the PICP²² and the ICTP²³ was obtained by a radioimmunoassay (Orion Diagnostica, Finland). According to the manufacturer, normal values are 50-220 µg/l for PICP and 1.7-5.0 mcg/l for ICTP, and the intra-assay and interassay coefficients of variation are 3% and 5% for PICP and 4% and 6% for ICTP. The kits for measuring PICP and ICTP were kindly supplied by Orion Diagnostica (Finland).

The free fractions as well as total Pyr and Dpyr were determined by high performance liquid chromatography. Normal values for healthy persons aged 22-64 years in our laboratory are free Pyr 11.3 µmol/mol creatine (range 5.9-36.2), free Dpyr 3.6 µmol/mol creatine (range 1.0-13.5), total Pyr 24.2 µmol/mol

creatinine (range 13.5–53.2), and total Dpyr 7.1 $\mu\text{mol/mol}$ creatinine (range 2.2–27.6). In our laboratory, the intra-assay coefficients of variation for pyridinolines was less than 10%, the interassay coefficient of variation less than 12.5%.²⁴

SAFETY VARIABLES

All patients were assessed at baseline and at 3, 6, 12, 18, and 24 months by the same observer. At these visits gastrointestinal and musculoskeletal side effects were investigated. A microfracture was defined as a moderate to severe pain in a lower extremity, which disappeared after discontinuation of the trial medication with objective changes on a bone scan or subsequent radiographs ('lower extremity pain syndrome').

STATISTICS

Statistical analysis was carried out with the Number Cruncher Statistical System (NCSS), version 5.1.

Data were analysed only if BMD had been measured at least twice. BMD at 6, 12, 18, and 24 months was compared with baseline within groups using paired *t* tests for data with a normal distribution and the Wilcoxon rank sum test for a skewed distribution.

The mean percentage change in BMD for the lumbar spine and hips in both groups was

Table 1 Demographic and clinical data on patients at baseline

| | Etidronate/placebo (n=24) | Etidronate/NaF (n=23) |
|--|---------------------------|-----------------------|
| Age (y) | 60 (17) | 56 (17) |
| Men | 9 | 5 |
| Women | 15 | 18 |
| Premenopausal | 5 | 3 |
| Postmenopausal | 10 | 15 |
| Height (cm) | 168 (8) | 165 (10) |
| Weight (kg) | 71 (12) | 66 (11) |
| RA | 12 | 11 |
| SLE | 6 | 4 |
| Other | | |
| Connective tissue disorder | 4 | 4 |
| COPD | 1 | 2 |
| Transplantation | 1 | 0 |
| Disease duration (y) | 9 (9) | 10 (10) |
| Corticosteroids, cumulative (g) | 10.7 (5.9) | 14.6 (14.9) |
| Corticosteroids, baseline (mg/day) | 16.9 (19.8) | 10.6 (4.2) |
| BMD, lumbar spine (g/cm^2) | 0.944 (0.167) | 0.804 (0.142)** |
| BMD, hips (g/cm^2) | 0.679 (0.194) | 0.6 (0.112) |

No significant differences between groups, except for BMD of lumbar spine at baseline (** $p < 0.01$). Data shown as mean (SD).

Table 2 Laboratory values at baseline for etidronate/placebo group and etidronate/NaF group

| | Etidronate/placebo | Etidronate/NaF |
|---|--------------------|----------------|
| Serum | | |
| Creatinine (50–140 $\mu\text{mol/l}$) | 106 (47) | 106 (32) |
| Calcium (2.20–2.60 mmol/l) | 2.41 (0.10) | 2.46 (0.18) |
| Phosphorus (0.80–1.50 mmol/l) | 0.94 (0.21) | 0.98 (0.18) |
| CRP ($< 8 \text{ mg/l}$) | 14 (23) | 13 (17) |
| ESR ($< 10 \text{ mm/h}$) | 30 (22) | 28 (23) |
| AP (27–93 U/l) | 60 (20) | 74 (33) |
| BAP (14–43 U/l) | 15.1 (8.3) | 22.6 (14.2) |
| Osteocalcin (12.9–55.9 ng/ml) | 15.3 (9.2) | 20.4 (10.7) |
| PICP (50–220 $\mu\text{g/l}$) | 103 (48) | 112 (34) |
| ICTP (1.7–5.0 $\mu\text{g/l}$) | 5.1 (2.6) | 5.6 (2.5) |
| 25 Vitamin D ($< 15 \mu\text{g/l}$) | 20.2 (10.6) | 21.9 (12.8) |
| Urine | | |
| Calcium ($< 0.50 \text{ mmol/mol creatinine}$) | 0.42 (0.30) | 0.33 (0.28) |
| Hydroxyproline ($< 30 \mu\text{mol/mol creatinine}$) | 14.3 (19.6) | 20.4 (9.1) |
| Pyridinoline, total (13.5–53.2 $\mu\text{mol/mol creatinine}$) | 55 (42) | 46 (23) |
| Deoxypyridinoline, total (2.2–27.6 $\mu\text{mol/mol creatinine}$) | 13.6 (9.8) | 12.4 (4.0) |

Data shown as mean with normal range in parentheses. No statistically significant differences at baseline were found between the two groups.

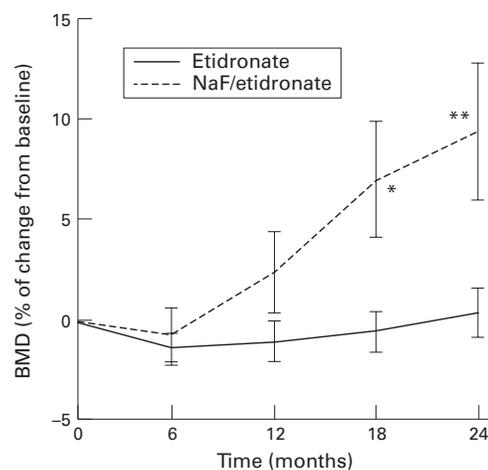


Figure 1 Effect of NaF/etidronate compared with that of placebo/etidronate on bone mineral density of the lumbar spine in corticosteroid treated patients with established osteoporosis. * $p < 0.05$, difference in changes between groups; ** $p < 0.01$, difference in changes between groups.

calculated, and the mean differences with respect to baseline values between both groups were compared by means of unpaired *t* tests; in the case of a skewed distribution with Mann-Whitney U tests.

For vertebral deformities, clinically manifest vertebral fractures, peripheral fractures, withdrawals and related adverse events, the differences in frequency between groups were compared by means of Fisher's exact test. A *p* value of < 0.05 was considered to be statistically significant. No adjustment was made for multiple comparisons.

Results

Tables 1 and 2 show the characteristics of both patient groups. The differences between the groups at baseline were not significant, except for the BMD of the lumbar spine, which was lower in the NaF/etidronate group ($p < 0.01$).

The trial was completed by 20 of 24 patients receiving only etidronate and 20 of 23 NaF/etidronate treated patients. In the etidronate group, two patients stopped after six months because of other severe diseases (pancreas carcinoma and encephalitis). Two patients in the etidronate group and one in the NaF/etidronate group stopped after one year because they no longer wanted to travel to Utrecht for the BMD measurements. In the NaF/etidronate group one patient died after 18 months of pulmonary embolism and one patient stopped after six months because of incomplete fractures at the knee.

ONE YEAR AFTER TREATMENT

The BMD of the lumbar spine had not changed significantly in either group: +2.3% (95% confidence intervals (CI): -1.8% to +6.4%) for the NaF/etidronate group and -1.1% (95% CI: -3.2% to +1.0%) for the etidronate group. The difference in the changes in BMD between the groups was +3.4% (95% CI: -1.0 to +7.8%). Figure 1 shows the changes in BMD of the lumbar spine.

Table 3 Markers of bone formation and bone resorption during two years of treatment with etidronate/placebo or etidronate/NaF in patients with established osteoporosis, treated with corticosteroids

| | Baseline | 3 months | 6 months | 12 months | 18 months | 24 months |
|------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| BAP (placebo) | 15.1 (8.3) | 14.2 (5.6) | 17.3 (10.2) | 15.0 (5.3) | 15.8 (5.8) | 16.0 (5.1) |
| BAP (NaF) | 22.6 (14.2) | 21.2 (9.2) | 25.4 (14.0) | 28.3 (13.4) | 24.8 (12.7) | 25.2 (14.5) |
| Osteocalcin (placebo) | 15.3 (9.2) | 17.8 (20.6) | 13.6 (7.0) | 16.9 (11.7) | 16.0 (7.4) | 15.8 (7.3) |
| Osteocalcin (NaF) | 20.4 (10.7) | 18.8 (8.1) | 21.6 (12.7) | 20.3 (9.9) | 18.3 (6.7) | 19.8 (10.0) |
| Pyridinoline (total, placebo) | 55 (42) | 53 (41) | 51 (38) | 46 (19) | 42 (20) | 40 (21) |
| Pyridinoline (total, NaF) | 46 (23) | 45 (27) | 50 (28) | 44 (18) | 46 (23) | 49 (25) |
| Deoxypyridinoline (total, placebo) | 13.6 (9.8) | 11.1 (7.5) | 9.2 (5.6) | 10.2 (4.7) | 9.8 (5.8) | 10.5 (6.0) |
| Deoxypyridinoline (total, NaF) | 12.4 (4.0) | 10.1 (5.4) | 12.5 (5.7) | 11.9 (6.1) | 12.6 (7.7) | 15.6 (16.7) |

No statistically significant differences in comparison with baseline in both groups. Data shown as mean (SD).

The BMD of the hips did not change significantly in either group: -1.0% (95% CI: -3.9% to $+1.9\%$) for the NaF/etidronate group and -2.9% (95% CI: -5.8% to $+0\%$) for the etidronate group. The difference in the changes in BMD between the groups was not significant: $+1.9\%$ (95% CI: -2.0% to $+5.9\%$). Figure 2 shows the changes in BMD of the lumbar spine.

TWO YEARS AFTER TREATMENT

The BMD of the lumbar spine had increased in the NaF/etidronate group by $+9.3\%$ (95% CI: $+2.3\%$ to $+16.2\%$, $p < 0.01$) and remained unchanged in the etidronate group ($+0.3\%$ (95% CI: -2.2% to $+2.8\%$)). The difference in the changes between groups was $+8.9\%$ (95% CI: $+1.9\%$ to $+16.0\%$, $p < 0.01$; fig 1). In absolute values, BMD increased from 0.804 (0.142) g/cm^2 to 0.867 (0.135) g/cm^2 in the NaF/etidronate group ($p < 0.01$), and remained unchanged in the etidronate only group: 0.944 (0.167) to 0.944 (0.157) g/cm^2 .

No significant changes in the BMD of the hips were observed after two years in the NaF/etidronate group: -2.5% (95% CI: -6.8% to $+1.8\%$) while in the etidronate group it had decreased significantly: -4.0% (95% CI: -6.6% to -1.4% ; $p < 0.01$). The difference between the groups was not significant: $+1.5\%$ (95% CI: -3.4% to $+6.4\%$; fig 2).

In absolute values, BMD decreased from 0.696 (0.193) g/cm^2 to 0.665 (0.171) g/cm^2 in the etidronate only group ($p < 0.01$), and

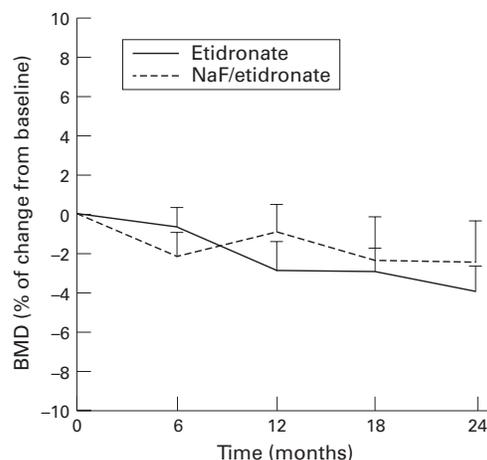


Figure 2 Effect of NaF/etidronate compared with that of placebo/etidronate on bone mineral density of the hips in corticosteroid treated patients with established osteoporosis. Difference in changes between groups not statistically significant.

remained unchanged in the NaF/etidronate only group: 0.60 (0.112) to 0.573 (0.105) g/cm^2 .

Peripheral fractures occurred in the first year in four patients of the NaF group (two ankle and two proximal tibia fractures) and in one patient (wrist fracture) of the placebo group. In the second year four peripheral fractures occurred in each group (in the NaF group: three hip and one distal tibia fracture; in the etidronate only group: two hip and two ankle fractures). New vertebral deformities were observed in the first year in four patients from both groups and in the second year in three patients of the NaF group and none of the patients of the placebo group (difference not significant). Clinically manifest vertebral fractures were observed only in the first year in two of the NaF/etidronate treated patients and three of the etidronate treated patients.

All four markers of bone formation (AP, BAP, OC, and P1CP) were higher at baseline in the NaF/etidronate group than in the etidronate group, but this difference was not significant. During follow up, there was a tendency toward an increase (not significant) in AP and BAP (table 3) in the NaF treated patients.

There was no significant difference between the markers of bone resorption at baseline. In the etidronate group, there was a tendency toward a decrease (not significant) in urinary excretion of pyridinolines and serum ICTP during treatment, which was absent in the NaF/etidronate group (table 3).

CRP and ESR both gradually decreased during the study in both groups (data not shown). Daily dose of corticosteroids also gradually decreased in both groups (data not shown). Although the differences were not significant, the ESR was higher in the NaF/etidronate group, while the daily dose of corticosteroids was higher in the etidronate group.

Discussion

This study is the first randomised, double blind, placebo controlled trial to investigate the effect of NaF given in addition to cyclical etidronate on the BMD of the lumbar spine and hips in corticosteroid treated patients with established osteoporosis. Intervention is necessary in these patients, because they are at high risk for new manifestations of osteoporosis, because both the use of corticosteroids⁶⁻⁸ and the existing fracture(s)⁹ predispose to (further) osteoporotic fractures.

In this study, the effect of two years of combination treatment with NaF and cyclical etidronate on the BMD of the lumbar spine (+9.3%) was superior to that of cyclical etidronate alone (+0.3%). After two years the difference in the change in the BMD of +8.9% for the NaF group is larger than that found in a non-randomised study¹⁵ of corticosteroid treated patients (BMD of lumbar spine increased +4.2% after 18 months of treatment with monofluorophosphate) and comparable to that determined in a retrospective study¹³ of both NaF and corticosteroid treated patients (BMD increased +15% after three years). Moreover, the gain in bone mass is comparable to that found in a recent study²⁵ of postmenopausal women not treated with corticosteroids (increase in BMD of 4 to 5% per year during four years of treatment with 25 mg NaF twice daily).

The gain in BMD of +0.3% after two years in the etidronate only group is somewhat disappointing. In our opinion, this is related to the underlying disease for which the corticosteroids are described. In a comparable study,¹⁶ in which patients with temporal arthritis were included, an increase in BMD of 1.4% was observed. We think that etidronate seems to be slightly less effective in our study, because we have included patients with severe rheumatoid arthritis and polymyositis, who are much more immobilised than patients with temporal arteritis.

Bone loss at the hips in the etidronate group (-4.0%, $p < 0.01$) was larger than in the NaF/etidronate group (-2.5%, not significant), but the difference in changes in BMD between the two groups was not significant. The difference in the effect of drugs on the BMD of the lumbar spine and the hips was also observed in earlier studies of corticosteroid treated patients with bisphosphonates^{16,17} and calcitriol.²⁶ It is thought that this difference is probably related to the high proportion of cortical bone in the hips; in the spine trabecular bone, which is metabolically more active, predominates. Although recently a positive effect of cyclical etidronate on the hips was described for corticosteroid treated patients,¹⁸ most (anti-osteoporotic) drugs seem to affect the BMD of the spine rather than the hips.

One of the drawbacks of this study is that despite randomisation, BMD of the lumbar spine was significantly lower (difference: 12%) at baseline in the NaF/etidronate treated patients group than in the etidronate group. Because a decrease in BMD of 1 SD is associated with an increase in fracture risk of 1.5 to 2,²⁷ and a decrease in bone mass of 1 SD is comparable with a bone loss of 10%, the risk of fractures was roughly doubled for patients taking NaF/etidronate.

During the two year study period, no significant difference was observed between the two groups in the number of fractures. This was not unexpected, because of the comparatively small size of both groups. However, the number of fractures was somewhat higher

among the NaF treated patients, which is probably related to the difference in BMD at baseline.

During NaF treatment some markers of bone formation remained unchanged (OC and P1CP); there was a tendency toward an increase in AP and BAP (not significant). This is in contrast with the results of our parallel study, in which the effect of NaF versus placebo was studied in corticosteroid treated patients without established osteoporosis²⁸; in that study both OC and BAP were increased. This discrepancy is probably related to higher baseline values for all four markers of bone formation in the NaF group than in the placebo group (although the differences were not statistically significant).

In the etidronate group, ICTP, Pyr, and Dpyr all showed a tendency to decrease during treatment, indicating that bone resorption is decreased during treatment with cyclical etidronate. Urinary excretion of hydroxyproline remained unchanged in these patients, which shows that this is not a sensitive marker of changes in bone resorption.²⁹ Markers of bone resorption did not decrease in the NaF/etidronate group. We suggest that the effect of etidronate on bone resorption is neutralised by NaF, whereby its bone formation stimulating effect may lead to a secondary increase in bone resorption.

The two most important side effects of NaF are gastrointestinal disturbances and incomplete fractures ('the lower extremity pain syndrome'). Gastrointestinal symptoms (epigastric pain, nausea, and vomiting) are thought to be elicited by a direct irritating effect of fluoride on the gastric mucosa. Earlier, gastrointestinal symptoms were reported in 39%^{30,31} of the patients treated with NaF. However, gastrointestinal side effects occur less frequently when enteric coated sodium fluoride tablets are used.³² In this study, none of the 23 NaF treated patients reported gastrointestinal complaints.

The mechanism of the lower extremity pain syndrome is not fully understood. This syndrome was observed in a high proportion (54%) of postmenopausal women treated with alternating 90/60 mg doses of NaF (not enteric coated).³¹ In this study, we observed the lower extremity pain syndrome in only one patient: a 20 year old woman who took corticosteroids because of a renal transplant. At baseline, she had a serum creatinine of 138 $\mu\text{mol/l}$ (upper level in our laboratory: 140 $\mu\text{mol/l}$). In this patient high serum fluoride concentrations were probably reached (her creatinine clearance was < 40 ml/min), which also shows that incomplete fractures are probably dose related side effects of fluoride treatment.

During the study period, the mean daily dose of corticosteroids was higher in the etidronate only group but ESR and CRP were higher in the NaF/etidronate group; these differences were small and not statistically significant. Because bone loss is related to both the daily dose of corticosteroids^{1-4,6} and activity of the underlying disease,³³ which is reflected

by ESR and CRP, we suggest that these imbalances may neutralise each other.

The pathogenesis of postmenopausal osteoporosis is different from that of corticosteroid induced osteoporosis. In postmenopausal osteoporosis bone formation and to a greater degree bone resorption are generally increased,³⁴ so that anti-resorption therapy seems to be a logical strategy. In corticosteroid induced osteoporosis inhibition of bone formation plays a key part in the pathogenesis.¹⁰⁻¹² Thus, agents that stimulate bone formation seem promising for corticosteroid induced osteoporosis. At the moment fluoride is the only bone formation stimulating drug that can be given orally.

The 'ideal' drug to counteract (corticosteroid induced) osteoporosis must be safe and effective, which means that a positive effect on fracture incidence must be proved. Because a decrease in BMD is a major risk factor for fractures,²⁷ it is concluded in the recently developed FDA guidelines for anti-osteoporotic drugs that, in the absence of an unequivocal positive effect on fracture incidence, clinical decisions or guidelines should be based on studies with BMD as (second best) end point.³⁵ However, there is some doubt about the relation between an increase in BMD and increased bone strength in NaF treated patients.³⁶ In postmenopausal, not corticosteroid treated, women an increase in the BMD of the lumbar spine and a decrease in vertebral fracture rate were observed during treatment with 40-60 mg NaF daily.^{30,37} In another study,³¹ an increase in the BMD of the lumbar spine was accompanied by an increase in the number of peripheral fractures. In that study the doses of NaF were probably too high: 60 and 90 mg on alternating days. Moreover, NaF was not given as enteric coated tablets, probably leading to high (toxic) peak serum concentrations of fluoride. In a follow up study,³⁸ it seemed that fractures predominantly occurred in patients on the higher doses of NaF. Recently,²⁵ an increase in BMD of 4% to 5% per year and a decrease (-75%) in the vertebral fracture rate were observed after four years of treatment with a relatively low dose of NaF: 25 mg twice daily. These data^{25 30 31 37 38} suggest that the efficacy and side effects of NaF are dose related.^{39 40}

In summary, the effect of combination treatment with NaF and etidronate on the BMD of the lumbar spine in corticosteroid treated patients with established osteoporosis is superior to that of etidronate alone. Side effects were scarce and a significant change in fracture rate was not observed. Further studies are needed to determine the effect of the combined use of NaF and cyclical etidronate on fracture incidence for corticosteroid treated patients.

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