Fluoride Therapy for Vertebral Osteoporosis

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Vertebral osteoporosis is characterized by a predominant atrophy of spongy bone inducing non-traumatic vertebral fractures. Because a low bone mass is the major determinant of fracture risk, the ideal therapy for established vertebral osteoporosis should increase trabecular bone mass substantially, thereby decreasing the risk of new crush fractures. This ideal treatment should also be capable of restoring the normal architecture of bone in order to maintain its mechanical properties. Treatments acting by decreasing bone resorption can maintain existing bone mass or protect spongy bone architecture, but cannot substantially increase bone mass in order to decrease the occurrence of new vertebral fractures. Of the antiresorptive drugs, calcitonin has never been shown capable of reducing vertebral fracture rate in established osteoporosis, and the promising results recently obtained with an intermittent cyclical treatment with etidronate given for 2 years in osteoporosis (1) have not been confirmed by a follow-up of 346 patients during the third year of treatment with the drug.

In contrast, regimens that stimulate bone formation have the potential of increasing bone mass, and fluoride is one of the most effective of these regimens because of its ability to increase the osteoblast cell population. Fluoride was proposed as a curative therapy for vertebral crush fracture syndrome 30 years ago, and this idea was suggested by the massive increase in trabecular bone density of the axial skeleton that characterizes skeletal fluorosis radiologically and the low prevalence of osteoporosis in areas with moderately high fluoride concentrations in drinking water. Since 1961, several prospective open studies have shown that fluoride salts (sodium fluoride or monofluorophosphate) are effective in increasing trabecular bone mass. This was shown first by radiological techniques, then by histomorphometric analysis of iliac bone biopsies, and by measurements of the mineral bone density of the axial skeleton using dual photon absorptiometry, quantitative computed tomography, or neutron activation analysis. The stimulating effect on bone formation was confirmed by the increase in serum osteocalcin levels. These data led to a general agreement that sodium fluoride, combined with adequate calcium supplementation, has an anabolic effect on vertebral bone mass, and fluoride therapy has been approved for the treatment of established vertebral osteoporosis in nine European countries (Aus-
Uncertainties persisted, however, about the effectiveness of this treatment in decreasing the vertebral fracture rate, the effects on the risk of non-vertebral fractures related to the changes induced in cortical bone mass, the incidence of side effects limiting the clinical usefulness of fluoride treatment, especially gastrointestinal disorders and lower extremity pain syndrome. The statement published after the Consensus Development Conference held at Aalborg, October 3-4, 1987, concluded (2): "Fluoride may be used to increase trabecular bone mass in patients with severe vertebral osteoporosis. It is the only agent that has been shown to have a sustained effect on the formation of trabecular bone, both at appendicular and at axial sites. . . . Whether treatment with fluoride reduces the rate of vertebral fracture is not known. Prospective controlled studies now in place should help clarify this issue. . . . The optimum dose and duration of fluoride treatment are not known, but the duration should probably not exceed five years."

Four years after this statement, several new studies have been achieved and it is possible to answer, at least in part, most of the questions raised in 1987. These recent advances consisted first of the results of two large clinical prospective controlled trials carried out in France (3) and in the United States (4), both of which analyzed the risk–benefit ratio of fluoride–calcium combined therapy in established vertebral osteoporosis. These two studies using different doses reached different conclusions and will be detailed below. In addition, the Proceedings of the International Workshop on Fluoride and Bone held at Niagara-on-the-Lake, October 12-15, 1988, and published as a supplement of the Journal of Bone and Mineral Research in March, 1990, included 32 papers emphasizing in particular the importance of both the dosage and the bioavailability of fluoride salt preparations (sodium fluoride and monofluorophosphate), discussing the effects of fluoride on bone tissue and bone cells and the mechanisms of fractures in osteoporotic patients treated with fluoride (5). Moreover, in these last 3 years several papers on fluoride have been published in specialized journals and many abstracts presented in large international conferences, including the 3rd International Symposium on Osteoporosis held in Copenhagen, October 14–20, 1990, and where more than 20 studies on fluoride have been discussed.

**Efficacy: Influence of Dose and Bioavailability on the Changes in the Vertebral, Fracture Rate, and in Bone Density**

Table 1 summarizes the main characteristics of the target population and the main results from the French INSERM collaborative study (3), the Mayo Clinic study (4), and also the 4-year study carried out at the Henry Ford Hospital in Detroit (6) with the same daily dose of sodium fluoride (NaF) as the one given in the Mayo Clinic.
TABLE 1. Main characteristics and results of three recent controlled studies

<table>
<thead>
<tr>
<th></th>
<th>Mamelle et al., 1988 (3)</th>
<th>Riggs et al., 1990 (4)</th>
<th>Kleerekoper et al., 1990 (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>C (other therapies)</td>
<td>C (1,500 mg Ca) P; DB</td>
<td>C (1,500 mg Ca) P; DB</td>
</tr>
<tr>
<td>Daily dose NaF (mg)</td>
<td>50 (Osteofluor 25)</td>
<td>90 day 1 60 day 2 mean: 75</td>
<td>75 (90–60)</td>
</tr>
<tr>
<td>Preparation</td>
<td>Enteric-coated tablets</td>
<td>Nonenteric coated capsules</td>
<td>Nonenteric coated capsules</td>
</tr>
<tr>
<td>No. patients enrolled</td>
<td>446</td>
<td>202</td>
<td>84</td>
</tr>
<tr>
<td>Duration of treatment (yrs)</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Effect on vertebral fracture rate</td>
<td>Significant reduction (−25%)</td>
<td>Nonsignificant reduction (−15%)</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Effect on nonvertebral complete fractures</td>
<td>Nonsignificant</td>
<td>Nonsignificant</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Effect on lumbar bone mineral density</td>
<td>Not determined</td>
<td>+35% (p &lt; 0.0001)</td>
<td>Not determined</td>
</tr>
<tr>
<td>Effect on radial shaft bone mineral content</td>
<td>Not determined</td>
<td>−4% (p &lt; 0.02)</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

C, controlled; P, prospective; DB, double blind.

Study. The French study used a low dose (50 mg/day) of NaF given as enteric-coated tablets for 2 years and showed a significant reduction in vertebral fracture rate. The Mayo Clinic study used a higher dose (75 mg/day) of NaF given as nonenteric-coated capsules for 4 years. With this dose the authors noted that the number of new vertebral fractures over the whole study period was not different in the NaF group and the control group receiving calcium. It must be emphasized that the analysis of vertebral x-rays in the French study was performed blindly in only a quarter of the patients, selected at random. Riggs et al., in a recent paper (4), questioned the results obtained in this study and suggested that the reduction in the vertebral fracture rate was not significant. After reanalysis of their data, the authors have confirmed that the 25% reduction in vertebral fractures after 2 years of treatment was significant, when calculated by the methods used by Riggs et al. (4). They calculated rates per person-year and found, between 0 and 24 months, 173 crush fractures per 360 patient years (rate: 0.48) in the NaF group, and 174 fractures per 272 patient year (rate: 0.64) in the non-NaF group. This 25% reduction is significant (chi square 15.8, p < 0.001).

The Mayo Clinic study has given rise to several recent comments, mainly calling into question the high mean daily dose (75 mg NaF), the preparation used (30 mg NaF nonenteric-coated capsules), and the duration of treatment (4 years) (8–10).
this study the daily fluoride ion dosage of 34 mg was 35% higher than the maximum
dose of 25 mg recommended by the status report published after the Workshop on
Fluoride and Bone held in Ontario, Canada, October 12–15, 1988 (11). Moreover,
the bioavailability of NaF contained in the nonenteric-coated 30-mg capsules used
in the Mayo Clinic study has been found much greater than that provided by enteric-
coated tablets containing the same amount of NaF (10): the C max was found to be
twice as high (21.3 vs. 10.1 μmol/L), the area under the curve 60% higher (85.2 vs.
53.5 μmol/L) and urinary output 100% greater (1.40 vs. 0.70 μmol/mg creatinine).
In addition, the differences in bioavailability remained the same between the enteric-
coated tablets and the nonenteric-coated capsules when they were both administered
concurrently with the calcium carbonate capsules used in the Mayo Clinic study (12).
If we take overall account of the high dose, the high bioavailability, and the long
duration of the study, the cumulative dose of fluoride taken up by bone can be
estimated to be more than 3 times as great as the total reached at the end of the
French INSERM study (3). It is well known that bone fluoride content increases
linearly with the duration of the treatment for an identical oral dose (13), and that
a high cumulative dose of NaF can induce severe mineralization defect in bone tissue.
Kleerekoper et al. (14) have recently shown that osteomalacia (defined as an osteoid
volume higher than 5% and a mineralization lag time longer than 100 days) was found
in 69% of 13 osteoporotic patients who had received 75 mg/day of NaF for a mean
duration of 42 months. It is likely that the increased vertebral fracture rate noted
during the third and fourth years of treatment in the Mayo Clinic trial could be due
to toxic effects of fluoride on bone tissue and bone cells, with a significant miner­
alization defect and also toxic effects on the osteoblast population, similar to those
found in skeletal fluorosis (15). The publication of data on bone fluoride content and
histomorphometric findings from the Mayo Clinic study will be of major interest.
The mean serum fluoride and urinary fluoride levels reported in Riggs’ paper (and
expressed in μmol/liter) do not reflect the actual levels present in patients, because
NaF administration was stopped 48 hours before the blood was drawn for serum
fluoride and 24 hours before the 24-hour urine was collected (BL Riggs, personal
communication).
If a mineralization defect is confirmed in the patients long term treated in the
Mayo Clinic trial, this could explain the absence of a significant relationship between
the increase in vertebral density and the changes in fracture rate reported by the
authors (16), because of the presence of marked abnormalities in bone quality. In
contrast, in a recent large study on 514 patients treated for a mean duration of 29
months with a dose of 29 mg elemental fluoride/day, Farley et al. (17) have shown
that the lumbar fracture rate was inversely related to spinal bone density measured
by quantitative computed tomography. Fluoride-treated patients exhibiting a sig­
nificant increase in lumbar bone density had a 70% reduction in lumbar fracture rate
compared to nonresponders. If we analyze the potential of fluoride therapy to restore
trabecular bone mass in light of the “fracture threshold” concept, it is important to
realize that a major increase in bone mass, even of 50% or 100%, will be unable to
achieve a protective effect on further vertebral fractures if the initial trabecular bone
volume is extremely low. In the Mayo Clinic study (4) where the mean lumbar bone mineral density (LBMD) was 0.77 g/cm² in the fluoride group, the 35% mean increase in LBMD only brought the mean value approximately to the level of the fracture threshold. This means that about 50% of patients after 4 years of treatment still had a LBMD lower than the “fracture threshold” value. It also means that any late intervention on bones where major rarefaction of trabeculae and near destruction of the trabecular network are already present is of little use in preventing further fractures. This should encourage earlier intervention in osteoporotic patients.

The reduction in vertebral fracture rate in osteoporotic patients treated long term with enteric-coated NaF tablets has recently been confirmed by two open studies by Franke and Hauch and Hodsman et al., both presented during the 3rd International Symposium on Osteoporosis (Copenhagen; October 14–20, 1990). Franke and Hauch (18) have treated 52 osteoporotic patients for 2 to 5 years with 60 to 80 mg NaF/day. The fracture rate was 750 fractures/1,000 patient years in the first year and fell to 96 in the second year and to zero in the third and fourth years. Hodsman et al. (19) have treated 55 patients with NaF in daily doses of 20 to 60 mg. Vertebral fracture rate was 318/1,000 patient years in responders and 632/1,000 in nonresponders during the interval between 18 and 36 months (p < 0.01). The patients classified as responders had an average change of 7% to 8% over baseline vertebral bone mineral density. During the first 18 months of treatment the vertebral fracture rate was identical in nonresponders and responders (576 and 578/1,000, respectively).

SIDE EFFECTS

All open studies have shown that fluoride therapy may induce side effects, particularly gastrointestinal and osteoarticular, and both appear to be dose-related.

Gastrointestinal

Gastrointestinal side effects occur in 10% to 40% of patients. They commonly include nausea and vomiting and, very rarely, anemia due to blood loss. In the French INSERM study using a low dose of enteric-coated Osteofluor tablets (3), the relative risk of gastrointestinal disorders (non-NaF/NaF) was found to be 1.08 (non-significant) after adjustment for a history of digestive disorders. In the Mayo Clinic study using a high dose and nonenteric-coated capsules (4), the fluoride-treated women had gastric symptoms 2.9 times more frequently than the women given placebo. In contrast, in a recent study using a slow-release sodium fluoride tablet (25 mg twice daily) given as an intermittent treatment for 3 out of 5 months, less than 15% of patients had adverse gastrointestinal reactions (20).

Osteoarticular

From published reports, transient lower extremity pain is experienced by 10% to 50% of treated patients. In the French study, episodes of osteoarticular pain were
frequent in both groups of patients followed for 2 years: 37% of fluoride-treated patients versus 30% of non-fluoride subjects (3). Pain in the ankle and foot were, however, noted significantly more often among fluoride-treated patients than in the non-fluoride group: 15% of patients in the NaF group compared with 5% in the non-NaF group had at least one episode of pain in the ankle and foot \( (p < 0.01) \). In the US study (4), lower extremity pain syndrome occurred in 37 patients receiving NaF and in five receiving placebo. About 10% of the episodes were bilateral. In a study comparing NaF (50 mg/day of Osteofluor) and monofluorophosphate (MFP, 200 mg/day), Delmas et al. (21) noted that the incidence of lower extremity pain related to stress microfractures was significantly higher with MFP than with NaF (34.5% vs. 15.4%, \( p < 0.05 \)). The number of episodes per patient years of treatment was also greater in the MFP group (36.8% vs. 12.5%, \( p < 0.01 \)). Patients who developed lower extremity pain had a greater increase in lumbar bone mineral density than those who did not. These differences have been shown to be related to a much better bioavailability of fluoride when given as MFP (100-mg effervescent tablet) than when given as a 25-mg enteric-coated tablet of NaF. In an open study using intermittent treatment with a slow-release fluoride preparation, Pak et al. found 14% of patients had rheumatic complaints (22).

Non-vertebral Fractures: Effects of Fluoride on Cortical Bone

Non-vertebral fractures—in particular hip fractures—have been found to be more frequent in patients treated with fluoride in some uncontrolled studies (23,24), whereas in other studies the incidence of these fractures has not been affected (3,25). They occurred with equal frequency in the two groups followed for 2 years in the INSERM French trial (3): 24 fractures were noted in the NaF group (including six hip fractures) and 22 in the non-NaF group (including four hip fractures). In the total population of 446 patients, 28 fractures were reported in each group, including seven hip fractures in the NaF group and eight in the non-NaF group. In the Mayo Clinic trial (4), the number of complete fractures was not significantly different between the two groups, with seven hip fractures (including one traumatic fracture) in the NaF-calcium group and three in the calcium group. In the Henry Ford Hospital trial (6), two hip fractures occurred in the calcium group and three in the NaF-calcium group. In the Mayo Clinic trial, the bone mineral density decreased by 1% per year in the shaft of the radius containing predominantly cortical bone (minus 4% in 4 years; \( p < 0.02 \)). This confirms the results obtained by Hodsman and Drost (26) with 60 mg/day of NaF given for 29 months on average. They reported that cortical bone density in the forearm decreased by an alarming 7.7%/year. This was not the case in our first study using 50 mg/day of NaF for 2 years, where radial bone mineral content did not change (27). Schulz et al. (28) have recently evaluated the effect of fluoride therapy on cortical thickness in 52 osteoporotic patients by separately measuring cortical and trabecular densities in the first lumbar vertebra with quantitative computed tomography. They found an increase in trabecular bone density of 3.20
± 1.87 mg/ml (value ± SD) per month and a corresponding increase in cortical bone density of 3.17 ± 2.14 mg/ml per month. A paired t test analysis showed that the differences between the trabecular and cortical rates of increase were not significant. In addition, Strauss et al. (29), studying 28 patients with postmenopausal osteoporosis for an average of 2.2 years after the discontinuation of NaF therapy given for an average of 4.6 years at a mean dose of 44 ± 9 mg/day of NaF (enteric-coated), have shown that the non-vertebral fracture rate was not increased. While on NaF, this non-vertebral fracture rate was 154 fractures/1,000 patient years and was not significantly different after NaF was discontinued (129 fractures/1,000 patient years). In the meantime, they have shown that the increase in mineral mass, expressed as the calcium/bone index (CaBI), was largely maintained after NaF was discontinued.

In a recent study, Pouilles et al. (30) have analyzed the effects of a daily treatment with 50 mg NaF (enteric-coated Osteofluor 25), 1 g calcium, and 400 IU vitamin D₂ on both vertebral and femoral bone densities in 52 postmenopausal osteopenic women. They found a 5.5% increase in vertebral bone density at 24 months in the NaF group and a 1.8% decrease in the control group, while femoral neck and trochanteric bone mineral density declined by 2% to 3%, without any difference between the NaF and control groups.

CONCLUSION

Since 1987, the results of two large controlled trials made in the United States (4,6) have shown that high daily doses of sodium fluoride (75 mg) given in nonenteric-coated capsules, providing high bioavailability of fluoride, do not provide a valid benefit-to-risk ratio in 4 years of treatment of established vertebral osteoporosis. They had a limited efficacy and induced a large number of side effects, with histological evidence of a mineralization defect in two-thirds of the patients (14). This corresponds to a cumulative dose delivered to bone that is about 3 times greater than the one provided by a 50-mg daily dose given in enteric-coated tablets for 2 years. Bone fluoride content is known to increase linearly with the duration of treatment in osteoporosis or with the time of exposure in toxic skeletal fluorosis, and the incidence of osteoarticular side effects is clearly dose-dependent, as shown by the analysis of the recently published reports. In contrast, all these studies—including two recent British open studies (31,32)—show that low doses (50 mg) of sodium fluoride given in enteric-coated tablets, providing much lower bioavailability of fluoride than nonenteric-coated capsules, are beneficial when given for 2 or 3 years in osteoporotic patients and have an acceptable incidence of side effects. These low doses are capable of reducing the vertebral fracture rate without increasing cortical bone loss and the non-vertebral fracture incidence. This has still to be proven for fluoride preparations having a higher bioavailability and/or containing a higher amount of fluoride ion, such as monofluorophosphate preparations.

Until recently, the message concerning the benefit-to-risk ratio of fluoride therapy in vertebral osteoporosis has been rather confusing, because "fluoride" has been
taken into consideration globally without taking into account the fact that quite different therapeutic strategies have used different fluoride salts, different doses, different preparations providing very different bioavailabilities of fluoride ion, and different durations of treatment. NaF given as enteric-coated tablets and used at a daily dose of 50 mg, or MFP given as effervescent tablet and used at a daily dose of 150 to 200 mg, meet the conditions of dosage and bioavailability that correspond to an efficient and safe therapeutic window.

Because most studies with those compounds have lasted 2 years, the recommended duration of the treatment could be provisionally limited to 2 years. They should be given in combination with calcium supplements, while taking into account the classical contraindications: renal failure, osteomalacia, and previous hip fracture. The treatment should be prescribed as soon as possible after the first vertebral crush fracture.

REFERENCES

FLUORIDE AND OSTEOPOROSIS


DISCUSSION

This chapter was part of the Round-Table Conference on prevention of osteoporosis. Please refer to the round-table discussion, page 187.