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Original Article

A Randomized Trial of Sodium Fluoride as a Treatment for Postmenopausal Osteoporosis

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Abstract. The anti-fracture efficacy of sodium fluoride (NaF) was evaluated in 84 postmenopausal white women with spinal osteoporosis. The dose of NaF used was 75 mg/day and all patients in this prospective, randomized, double-blind, placebo-controlled clinical trial received calcium supplements (carbonate salt) 1500 mg/day in addition to participating in a structured physical therapy program. For each of the outcome measures (change in stature, change in cortical bone mass in the forearm and development of new vertebral fractures determined by change in vertebral morphometry and by scintigraphy) there was no significant difference between the fluoride or placebo treated groups. Side effects, predominantly gastrointestinal symptoms and the development of the painful lower extremity syndrome, occurred significantly more frequently in the fluoride group ($P<0.05$). Peripheral fractures were not more frequent in the fluoride group. We conclude that, in the dose and manner used in this study, NaF is no more effective than placebo in retarding the progression of spinal osteoporosis. There is no role for NaF in the treatment of osteoporosis outside the confines of clinical research.

Keywords: Clinical trial; Fluoride; Osteoporosis; Vertebral fracture

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Introduction

Sodium fluoride has been shown to increase spinal bone mass and cancellous bone volume in the ilium of patients with osteoporosis and a reduction in vertebral fracture rate would be expected. This has been suggested from uncontrolled studies [1,2] but in recently published controlled clinical trials the vertebral fracture rate was either the same [3,4] or greater [5] in sodium fluoride treated patients.

In this paper we report the results of a double-blind, placebo-controlled, prospective clinical trial examining the safety and efficacy of 75 mg/day of sodium fluoride plus 1500 mg/day of calcium in reducing the vertebral fracture rate in 84 white women with postmenopausal osteoporosis.

Methods

Patients

The trial was restricted to white women aged 45 to 75 years at entry into the trial who were at least one year post-menopause. All had one or more vertebral compression fractures or two or more non-contiguous vertebral wedge deformities readily apparent on lateral spine radiographs and gave a history of none or trivial trauma at the time of fracture. Patients who had previously received therapy with sodium fluoride for osteoporosis were excluded from the trial as were patients who were on estrogen therapy for osteoporosis. Causes of bone loss other than age and menopausal status were syste-

matically excluded in every patient. All patients provided written informed consent.

When the presence of osteoporotic vertebral fractures had been confirmed radiographically all patients were instructed in an active physical therapy/rehabilitation program which was continued throughout the trial. Upon completion of all baseline measurements and provision of informed consent all patients began therapy with calcium carbonate sufficient to provide 1500 mg of supplemental calcium per day. This dose was also continued throughout the trial. Six months later patients were randomized to receive sodium fluoride 30 mg orally alternating between twice and three times a day or to receive a matching number of placebo capsules. Thus the initial average daily dose of study medication (sodium fluoride or placebo) was 75 mg/day. The study was conducted in a double-blind fashion with both the subjects and the investigators unaware of whether the patient was receiving active medication or placebo. Patients were to be followed for 48 months.

Side effects reported by the patient which were considered by the investigators to be possibly related to the study medications resulted in temporary interruption of therapy (sodium fluoride or placebo) until the symptoms subsided or for six weeks (whichever was the shorter period) and reinstituted at a dose of 30 mg/day gradually increasing, where possible, to full dosage over the next three to four weeks. All side effects and results of all laboratory studies were also reported to a study monitoring committee which had no direct contact with the trial participants. If this committee decided a reported side effect or laboratory result warranted temporary or permanent interruption of therapy this information was transmitted to the patient via the investigators. To avoid unblinding, investigators were to be notified to change the dose in some placebo patients. All study medications (calcium carbonate, sodium fluoride and placebo) were supplied by Mericon Industries, Inc. Peoria, IL, 61615.

Outcome Measures

The trial was designed to determine the anti-fracture efficacy and safety of sodium fluoride with lesser emphasis placed on gaining more understanding of the mechanism of action of the study drug. Accordingly only those measures related directly to efficacy and safety are reported here.

Bone mass was monitored at six-month intervals using single-photon absorptiometry of the non-dominant radial mid-shaft.

Standing shoeless height was measured to the nearest millimeter every six months using a Harpenden Stadiometer (Holtain Ltd., Crymmych, Pembs., UK). This instrument has a coefficient of variation of 0.15% (DA Nelson, unpublished data).

Radiographs of the thoracic and lumbar spine in the lateral projection were obtained at the end of six and twelve months after randomization and annually thereafter. Every effort was made to standardize the radiographic procedure with all serial X-rays taken with the tube at a fixed distance from the patient using the same kV and exposure time. A new fracture was defined as a reduction of one or more of these heights by 15% or greater from baseline [1]. If a new fracture was detected by this method then the baseline value was reset at the new (lower) value and recurrent fracture in the same vertebra was defined as a 15% or greater reduction in height from the new baseline. Vertebral fracture rate for each group was calculated per 1000 patient years of observation.

Radionuclide bone scans using 99mTc-MDP (methylene diphosphonate) as the tracer were obtained at baseline and every six months throughout the trial. A new fracture was defined as the appearance of an area of increased isotope uptake ('hot spot') over a vertebra that had been normal on the previous scan. 'Hot spots' were also detected in many patients over areas of the skeleton other than the vertebrae. When this occurred this was reported as a side effect of the medication and a radiograph of the affected area of the skeleton was taken as soon as the bone scan study was completed. The rate of occurrence of new vertebral fractures and non-vertebral 'hot spots' was calculated per 1000 patient years of observation.

Safety measures obtained every six months throughout the study consisted of an automated complete blood count and an automated 23-channel biochemical profile using standard procedures in the Department of Clinical Chemistry laboratory of Henry Ford Hospital.

Statistical Methods

At the beginning of the trial in 1981, the University of Michigan School of Public Health was the Statistical Center. The Statistical Center designed trial procedures, randomized patients, and monitored patient recruitment and follow-up. In 1986, the Statistical Center was moved to the new Division of Biostatistics and Research Epidemiology at Henry Ford Hospital. The trial was designed to test the one-sided hypothesis that fluoride and calcium therapy would reduce the vertebral fracture rate as compared with the placebo and calcium treated group with an initial assumption that the placebo group fracture rate would be 700 per 1000 person-years of follow-up. Also, at the time the study was designed, power was calculated under the assumption of a Poisson model with the variance estimate inflated (negative binomial distribution) to reflect the probable non-independence of fractures. With a sample size of 55 per group assuming a 50% decrease in fracture rate for the fluoride group (odds ratio = 2.0) and a one-sided α level of 0.05 the power of the test would be 90%

A stratified randomization scheme was used for the trial. Strata included age, bone formation rate and the initial number of vertebral fractures. Non-compliant

subjects, drop-outs and those who failed to finish the trial due to its termination were included in analyses where data were available. This intention-to-treat analysis guards against bias in the results by differential withdrawal of subjects from the two groups in our trial.

Baseline data were examined using Student's *t*-tests and chi-squared tests for nominal variables. Drop-out rates were compared using a log rank test. To measure compliance with the protocol both calcium, fluoride and placebo tablets were given out at each visit with instructions that the unused portion should be returned at the next visit. To assess compliance, patients were categorized as taking less than 75% or greater than 75% of their required total medication while on study. A chi-square test was used to compare groups.

Fracture rates were expressed as fractures per 1000 person-years. Confidence limits (95%) on the odds ratio comparing fluoride to placebo were calculated [6]. Follow-up was estimated using the average number of person-years follow-up over the vertebra studies in each patient. The odds ratios and confidence limits were also used to compare treatment and placebo groups on bone scan hot spots in both the lower and upper extremities. Change in height was analyzed using a weighted regression approach. A simple linear regression modelling change in height compared with time was generated for each subject and the resulting slopes (change in height) were used as the dependent variable in a weighted regression analysis [7] examining for group differences after adjusting for covariates (baseline fracture rate, bone formation rate, age and the single-photon absorptiometry absolute Z-score from peak adult bone mass). The covariates were chosen *a priori* (the first three were used in the stratified randomization) to adjust for possible imbalances between the two groups. Although the trial was designed to test a one-sided hypothesis as described above, to be consistent with current reporting methods all *P*-values reported are two-sided.

In all analyses, the results reflect all available data on the 84 patients who entered the trial, whether or not they completed the full four years of the study.

Results

Of 663 evaluated patients, 84 subjects were enrolled into the trial from August, 1981 through December, 1987. Of these patients, 38 were randomized to placebo and 46 randomized to fluoride. Baseline variables are described and the results of the group comparisons are summarized in Table 1.

Twenty-three subjects (9 placebo, 14 fluoride) finished the 48 month trial, 21 subjects (12 placebo, 9 fluoride) were active participants when the trial was ended. Twenty-two patients (9 placebo and 13 follow-up) left the trial but later agreed to a final follow-up visit. This visit occurred near the completion of the trial. Its timing varied in the sequence of visits for each subject. Follow-up data varied from full study information resulting from re-entry into the trial to acquisition of only a final radiograph. Eighteen subjects (8 placebo, 10 fluoride) quit participation in the study and were not available or declined a final follow-up visit. The median duration of follow-up was 30 months for both the placebo and the fluoride groups. A log-rank test indicated that the drop-out experience was similar in the two treatment groups ($P = 0.90$). For those taking their medication there was no difference in compliance with calcium. In the placebo group 78% compared with 62% in the fluoride group who were on medication took more than 75% of the total 1500 mg/day calcium required, ($P = 0.64$). There was a greater difference in compliance with fluoride, 72% placebo compared with 50% of the fluoride group who were on medication took greater than 75% of the total 75 mg/day required ($P = 0.06$). At every visit average urine fluoride values for the fluoride group were two to four times greater than values for the placebo group.

Of the 84 subjects in the trial, 75 had at least two

Table 1. Baseline comparisons

Variable	Placebo			Fluoride			*P*-value
	n	Mean	SD	*n*	Mean	SD	
Clinical variables							
Age (years)	38	67.9	5.8	46	66.2	5.9	0.18
Years postmenopausal	35	22.0	8.7	45	20.8	7.9	0.49
Height (cm)	38	156.3	7.4	46	155.9	6.8	0.28
Weight (kg)	38	65.7	16.4	46	65.2	12.3	0.88
Daily calcium (mg/day)	37	426.3	264.5	46	471.9	265.0	0.44
Single-photon absorptiometry							
Bone mineral/width (gm/cm^2)	38	0.51	0.07	46	0.54	0.09	0.16
Z-score (from peak adult bone mass)	38	−5.20	1.49	46	−4.65	1.85	0.14
Cancellous bone formation rate ($\mu m^3/\mu m^2/yr$)	35	11.7	11.5	46	11.8	10.1	0.97
Initial number of fractures	37	4.0	2.7	43	4.6	2.4	0.29

radiographs taken and could be evaluated for the occurrence of fracture. Seventy-four percent (31/42) of the fluoride group had at least one new fracture during the study while 67% (22/33) of the placebo group had new fractures ($P = 0.50$). A total of 147 new fractures were observed. The fracture rate was estimated to be 723 per 1000 person-years follow-up for the placebo group. This was lower than the estimated fracture rate in the fluoride group of 961 per 1000 person-years of follow-up. The resulting odds ratio of 0.75 (95% confidence limits 0.44–1.30) was not significantly different from one ($P = 0.31$), (Table 2). The fracture rate for the fluoride group was consistent for patients who had completed the trial (865), active patients (1292) and drop-outs (896).

We also observed an increased rate of fracture, identified by radiograph for the fluoride group at the initial 6-month follow-up visit for the study. The rates estimated by radiograph were 603 for placebo and 1233 for fluoride per 1000 person-years of follow up (Table 3). However, because the 6-month follow-up period is arbitrarily chosen, these results are considered descriptive.

The fracture rates defined by bone scan were lower than observed by X-ray for both groups. The rates were 119 for placebo and 243 for fluoride per 1000 person-years (Table 2). The odds ratio is estimated at 0.49 and is not significantly different from one ($P = 0.14$), (Table 2).

Bone scans also indicated an increased rate of non-vertebral lesions for the fluoride group (Table 4). There were very few lesions indicated in the upper extremities, two in the placebo and five in the fluoride group. In the lower extremities 132 lesions were identified with the rate (per 1000 person-years follow-up) in the fluoride group (936) being over three times that in the placebo group (302, Table 4).

Patient height showed a decrease of 0.3 cm per year in

Table 2. Vertebral fracture summary

Device	Group	*n*	Person–years	No. of fractures[a]	Fracture rate per 1000 person-years	Odds ratio	95% Conf. limit	*P*-value
Radiograph	Placebo	33	77.47	56	723	0.75	(0.44–1.30)	0.31
	Fluoride	42	94.71	91	961			
Bone Scan	Placebo	33	92.82	11	119	0.49	(0.19–1.28)	0.14
	Fluoride	42	111.13	27	243			

[a]Placebo group had 21 end plate deformities, 15 wedge and 20 compression fractures.
Fluoride group had 31 end plate deformities, 29 wedge and 31 compression fractures.

Table 3. Vertebral fractures by yearly intervals

Year[a]	Group	*n*	Follow-up	No. of fractures	Fracture rate per 1000 person-years	Odds radio	95% Conf. limit
0–0.5	Placebo	32	18.24	11	603	0.49	(0.15–1.64)
	Fluoride	36	19.46	24	1233		
0.5–1	Placebo	28	17.28	7	405	1.07	(0.31–3.77)
	Fluoride	36	21.21	8	377		
1–2	Placebo	29	21.99	20	909	0.88	(0.40–1.93)
	Fluoride	36	28.01	29	1035		
2–3	Placebo	20	17.65	7	397	0.64	(0.21–1.90)
	Fluoride	25	20.82	13	624		
3–4	Placebo	16	6.24	11	1763	1.12	(0.35–3.57)
	Fluoride	20	10.76	17	1581		

[a]Includes X-rays 3 months beyond upper range except first interval which extends 1.5 months.

Table 4. Non-vertebral lesions (hot spots) on bone scan

Location	Group	*n*	Follow-up (person-years)	Hot spots	Rate per 1000 person years	Odds ratio	95% Conf. limit	*P*-value
Upper extremities	Fluoride	42	111.13	5	45	0.48	(0.10–2.39)	0.37
	Placebo	33	92.82	2	22			
Lower extremities	Fluoride	42	111.13	104	936	0.32	(0.13–0.80)	0.02
	Placebo	33	92.82	28	302			

the placebo group and 0.4 cm per year in the fluoride group. There was no significant difference ($P = 0.30$). Bone mineral density in the forearm decreased at a rate of 0.0010 g/cm^2 per year in the placebo group and 0.0034 g/cm^2 per year in the fluoride group ($P = 0.36$).

In a comparison of the seven placebo and 12 fluoride treated patients who had both an initial and 36-month visit biopsy, no difference was detected in cancellous bone volume at study entry (15.2 ± 5.9, placebo; 13.0 ± 5.0, fluoride; $P = 0.40$). At the final visit, the fluoride group showed an increase in cancellous bone volume (12.0 ± 3.5, placebo; 20.4 ± 10.8, fluoride; $P = 0.03$).

The fluoride group had an increased number of gastrointestinal side effects (35% in fluoride group had at least one complaint compared with 16% in the placebo group, Table 5). Hot spots associated with pain sufficient to require a dose change were also observed in 16 fluoride patients and one placebo patient (Table 6).

Table. 5. Symptoms developing during the clinical trial

Type	Number (%) of patients		*P*-value
	Placebo (n=38)	Fluoride (n=46)	
Gastrointestinal symptoms[a]	6 (16)	16 (35)	0.05
Non-vertebral fracture	7 (3)	13 (13)	0.29
Osteomalacia	0 (0)	8 (17)	0.01

[a]Associated with dose changes.

Table 6. Lower extremities and side effects

Group	Hot spot with pain	Hot spot without pain	No hot spot with pain	No hot spot without pain	Total
Fluoride	16	12	7	7	42
Placebo	1	7	12	13	33
Total	17	19	19	20	75

Chi-square = 16.84; $P<0.002$.

The sample size of 75 for analysis of fracture rates represents 68% of the planned enrollment. Using the observed data and the original design criteria, altered by considering a two-sided test, the power of the study was 66%.

Discussion

We realize that the low recruitment and high drop-out rate limits the power of our study and the strength of the observations we have made. However, this is a problem common to most trials in this area [8]. There was no relationship between treatment assignment and dropping out of the study, underscoring the difficulty in conducting clinical trials in osteoporosis and why there is a paucity of drug therapies for osteoporosis with proven anti-fracture efficacy.

In 1984 Kanis and Meunier [9] reviewed the then available literature on sodium fluoride and concluded that 'major questions remain concerning the benefits, the risks of treatment, the optimal regimen and the identification of the population suitable for treatment'. Since then there have been three published reports of controlled clinical trials examining the anti-fracture efficacy of sodium fluoride in patients with PMO. Dambachet et al. [5] treated 15 patients with a slow-release preparation providing 80 mg/day of sodium fluoride. Compared with 13 matched patients treated with placebo they demonstrated that over a three-year period sodium fluoride increased trabecular bone density but also increased vertebral fracture rate. It is unclear from the report whether or not either group was given calcium supplements. The omission of calcium from the regimen may have contributed to this adverse result.

The large multi-center French study [3] was not placebo-controlled but the 466 patients were randomized to receive either sodium fluoride 50 mg/day or one of five 'non-sodium fluoride' therapies which were commonly prescribed by French physicians for the treatment of PMO. The authors could not demonstrate that the mean number of new crush fractures per year after 2 years of therapy was different between the two arms of the trial. However, using the product limit method of analysis, they did demonstrate that the patients on sodium fluoride were significantly less likely to develop a new crush fracture. Most recently, in a study that was conducted in parallel to our present study, Riggs et al. [4] were unable to demonstrate any therapeutic advantage of fluoride over placebo.

These studies together with the results we report here are in sharp contrast to reports from uncontrolled trials demonstrating a very marked reduction of vertebral fractures in patients receiving continuous [1] or intermittent [2] sodium fluoride. These differences can almost certainly be accounted for by the lack of appropriate controls in those trials. The controlled trials published to date have employed 50, 75 or 80 mg of sodium fluoride and a variety of formulations. The overwhelming evidence from these trials is that sodium fluoride in a dose as high as 75 mg has limited effectiveness in reducing the occurrence of new vertebral deformities in PMO. This does not rule out the possibility that a lower dose, or a different chemical form of fluoride, or different regimen of administration might produce different results.

This is a disappointing and quite surprising result particularly in light of the almost universal observation that sodium fluoride increases bone mass in postmenopausal osteoporosis (PMO). There are several possible explanations, with quite different implications, for this discrepancy. The initial bone mass may have been so low, that even if almost doubled, it would remain below the fracture threshold. The effect of sodium fluoride to

increase bone mass does not dissipate with time [4] as does that of calcitonin [10,11]. Thus, the duration of therapy may have been too short to have resulted in a clear-cut reduction in fracture rate. If this were so a trend towards reduction in vertebral deformity rate would be expected in the later years of the trials. This does not appear to be the case in the present study nor in any of the other controlled trials.

An alternative hypothesis is that the quality of new bone formed under the influence of sodium fluoride is abnormal. The initial bone formed in response to sodium fluoride is partly woven in texture, but such bone is gradually replaced by apparently lamellar bone. Much of the added bone is incompletely mineralized, and its effect on bone strength is uncertain.

Radionuclide bone scans at six-monthly intervals were initially included in the study protocol in the expectation that more new vertebral fractures would be detected than with radiographs alone. This was surprisingly not the case. While the overall results obtained with the bone scan and the radiographs were of a similar pattern, only a small fraction of the new vertebral deformities detected radiographically were associated with an increased isotope uptake. The biologic significance of these observations is uncertain, but the discrepancies were evident in both groups, suggesting that this is inherent to the osteoporotic process and not related to sodium fluoride therapy.

The serial radionuclide bone scans provided some insight into the lower extremity pain syndrome that complicates sodium fluoride therapy and may also shed some light on the mechanism of action of sodium fluoride. A significantly greater proportion of the sodium fluoride treated patients manifested localized areas of increased isotope uptake in the lower extremities (Table 4) and for both groups these lesions were uncommon in the upper extremities. This suggests that these lesions are a consequence of sodium fluoride therapy, but are not due solely to a systemic effect on skeletal metabolism, and require an interaction with load bearing. Many of the lesions were not associated with clinical symptoms (Table 6) and it is uncertain whether they represent a toxic or a beneficial effect of the drug [12]. Others have shown that when symptoms develop, they are accompanied by thin bands of sclerosis on radiographs at the site of symptoms, compatible with healing of incomplete stress fractures [13,14], and associated with local excess accumulation of osteoid [15]. In none of our patients did these lower extremity lesions proceed to complete fracture, and in keeping with our earlier report of a multi-center study [16] we did not confirm the suggestion by others [17,18] that sodium fluoride was associated with an increased incidence of hip fractures.

We disagree with the interpretation of Riggs et al. [4] concerning the clinical significance of these scintigraphic lesions in the peripheral skeleton. They too found that what we have termed lower extremity hot spots and they have termed incomplete fractures, were significantly more prevalent in the fluoride treated group. In neither study was there any difference between the two groups with respect to the occurrence of complete peripheral fractures. Since we are uncertain of the biologic significance of these lower extremity hot spots and none of them progressed to true fractures we have avoided using the term fracture to describe these lesions. Riggs et al. [4], on the other hand, have chosen to combine incomplete and complete fractures for analysis and concluded that sodium fluoride therapy is associated with an increased incidence of peripheral fractures. There is no apparent biological rationale for combining the data for analysis. Furthermore review of their data indicates almost complete discordance in the anatomic distribution of complete and incomplete fractures.

Gastrointestinal symptoms occurred more frequently in the fluoride group than in the placebo group (Table 5), as has been reported by most other investigators. While these symptoms can be relieved and are quickly reversible when therapy is interrupted, they assume greater clinical importance in the absence of antifracture efficacy of sodium fluoride.

The negative results of this report, and the other placebo-controlled trials of sodium fluoride therapy suggest that use of this drug outside the confines of a clinical research program should be discontinued, at least for the time being. It is disappointing to conclude that after almost 30 years since the original publication by Rich and Ensinck [19], the therapeutic potential of fluoride remains to be realized. It should be emphasized however that no other drug has the same salutary effect on bone mass as sodium fluoride. While research efforts to treat established osteoporosis will continue, the importance of appropriate and well-established methods of preventing postmenopausal osteoporosis must be emphasized.

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Book Review

Textbook of Performing Arts Medicine. *Edited by R. T. Sataloff, A. G. Brandfonbrener and R. J. Lederman.* Raven Press, New York. ISBN: 0-88167-698-S, 448 pp., $88.00.

The appearance of this textbook testifies to the need for information on the health needs and treatment of performing artists. Unfortunately, the present book does not fulfill this purpose.

Contrary to its title, the focus of this textbook is on classical musicians. In nine out of thirteen chapters, other performing arts are "lumped" together or bypassed as case after case of musicians' problems are described in-depth. While performers do share many common stresses, such as performance anxiety, there are marked differences in skills, training, career span, and injuries that deserve equal consideration. Actors, comedians, dancers, and singers are not the same as musicians. Thus, it is misleading to the reader to use one group to illustrate the health needs of all performers.

In the end, this book is valuable, in spite of its flaws, because it is the only one of its kind available today. Hopefully it will lead the way to more balanced and documented texts in the future. It would have been better titled "Textbook of Medical Problems in Musicians and Other Performers."

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