

1996

Letter to the Editor

Fluoride and the FDA: A Curious Case

To the Editor:

In the fall of 1995, Dr. Charles Pak and colleagues presented arguments that won them a unanimous recommendation by a Food and Drug Administration (FDA) advisory committee for the approval of slow-release sodium fluoride to treat postmenopausal osteoporosis.⁽¹⁾ It now seems that fluoride has come full circle from the disappointing results of the Mayo Clinic and Henry Ford Hospital trials of the mid-1980s.

It was not that long ago that I was asked to provide biomechanics advice for the FDA in their attempt to rewrite the guidelines for preclinical and clinical evaluation of osteoporosis drugs. This was 1992, and the FDA was concerned about the (then) recently published results from the fluoride trial at the Mayo Clinic, which were not encouraging.⁽²⁾ The new guidelines reflected this concern by incorporating additional requirements for evaluations of osteoporosis treatments: demonstrative improvement of bone strength in animal models and significant fracture prevention in clinical trials. Bone strength, rather than bone mass, was made the gold standard by which to evaluate new drugs. Of course there is an exception to every rule, and it appears now that fluoride could be the exception to the new FDA guidelines.

While Dr. Pak's group should be commended for their intelligent approach to fluoride therapy and their well-run clinical trials, one cannot help but be alarmed by the negative effects of fluoride on bone strength consistently demonstrated in animal models. In the past couple of years, there have been several reports on the effects of fluoride treatment in animals; in a study in minipigs, fluoride increased bone formation but decreased spinal bone tissue strength⁽³⁾; in a study in rats, fluoride increased spinal bone mass without improving bone strength⁽⁴⁾; and, in a recent study in our lab using rabbits, fluoride increased spinal bone mass but decreased vertebral strength.⁽⁵⁾

One of my colleagues pointed out that none of these animal studies accurately simulated the fluoride treatment regimen used by Dr. Pak. Maybe this is true, but many fluoride treatment regimens have been studied in animals, and I know of only two animal studies that have shown fluoride to increase bone strength (those studies were done by Rich and Feist⁽⁶⁾ and our laboratory⁽⁷⁾), but in subsequent studies we have been unable to replicate these results⁽⁸⁾. In all other studies, fluoride has either had no effect on bone strength or significantly decreased it. The animal results for fluoride, thus far, certainly do not meet the efficacy requirements put forth by the FDA.

In response to these arguments, my colleague suggested that animals may not be appropriate for studies of fluoride since fluoride does not seem to work in them (this seemed like a circular argument to me, but I heard him out), therefore fluoride should be studied in patients; bone strength can be measured in biopsy specimens. This is a reasonable approach, and Dr. Pak's group has made the argument that ultrasonic evaluation of biopsy specimens, as is done in their laboratory,⁽⁹⁾ gives a measure of bone quality. Unfortunately, there are a couple of drawbacks. First, the bone kinetics and mineral quality of the iliac crest, from which the biopsies come, is much different than other sites in the body, especially the femoral neck,⁽¹⁰⁾ so measurements on biopsies may not reflect changes in hip strength. Second, ultrasonic techniques measure bone elasticity, not bone strength. While elasticity and strength are well correlated in healthy bone, it is unclear whether elasticity measurements accurately reflect bone strength in fluoridic bone. In short, evaluation of bone strength in clinical trials is problematic. These data would be much stronger if they were backed by biomechanical efficacy in animal studies, as is recommended by the FDA.

The strongest argument made by Dr. Pak's group for the safety of slow-release fluoride therapy is their observation that the skeletal fluoride content measured in patient biopsies was only 2800 parts per million (ppm), on average, in bone ash. They reason that this is far less than the "toxic threshold" of bone fluoride, which they set at 7000 ppm. While I do not find their claim of a toxic fluoride threshold particularly convincing, there have been no published reports, to the best of my knowledge, that have shown a detrimental effect on tissue-level bone strength in young healthy animals with skeletal fluoride levels less than 4000–5000 ppm in bone ash (their argument is less strong for older animals⁽⁸⁾). One shortcoming of this argument, however, is that many elderly adults have fairly high bone fluoride levels under normal conditions, resulting from a lifetime of consuming fluoridated water and fluoride-supplemented dentifrices. Thus, it is possible that some patients will "overdose" with fluoride therapy because of their high baseline bone fluoride levels.

If the FDA is going to make an exception to its guidelines, slow-release fluoride is clearly an excellent candidate. However, I was under the impression that one of the central reasons for establishing the tougher safety guidelines was the concerns about bone quality effects brought on by fluoride trials. Thereafter, countless pharmaceutical companies have spent tremendous amounts of money for ex-

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haustive evaluation of osteoporosis drugs that have nowhere near the bone quality side effects of fluoride, yet fluoride was unanimously recommended for approval by the FDA Endocrinologic and Metabolic Drugs Advisory Committee.

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Reply Curious or Outstanding?

To the Editor:

The letter by Dr. Turner in response to our perspective⁽¹⁾ affords us an opportunity to emphasize the fundamental hypothesis upon which our treatment program with slow-release sodium fluoride (SR-NaF) is based, namely that the action of fluoride is biphasic, having positive effects on bone quality and structure at low fluoride exposure, but negative effects at high exposure.⁽²⁾ Our treatment was specifically designed⁽³⁾ to avert the toxic skeletal retention of fluoride in order to capture its beneficial effects.

Contrary to Dr. Turner's view, there is extensive literature supporting biphasic fluoride action on bone. In experimental animals, the bone strength improves at low fluoride dose,⁽⁴⁻⁸⁾ but deteriorates at high dose.⁽⁹⁾ In clinical trials, structural integrity and improved quality of bone^(10,11) were demonstrated with less bioavailable⁽¹²⁾ SR-NaF or a lower dose of plain NaF,⁽¹³⁾ but an abnormal picture was disclosed with treatments with more bioavailable fluoride preparations at usual or high dosage.⁽¹⁴⁻¹⁶⁾

We contend that the fluoride content of 0.28% bone ash found after 4 years of our treatment represents a subtoxic value. This value corresponds closely to 0.25%, at which a maximum improvement in bone quality was reported in fluoride-treated rabbits.⁽⁸⁾ We found normally mineralized

bone⁽¹¹⁾ of improved quality⁽¹⁰⁾ following treatment with SR-NaF, during which skeletal fluoride was kept considerably below 0.6-0.7% bone ash, which is believed to be the toxic threshold.^(2,17)

This toxic threshold is supported by disclosure of abnormal bone structure and quality when skeletal fluoride exceeds this value.^(14,15,18) In contrast, as Dr. Turner points out, there is no evidence for a "detrimental effect on tissue-level bone strength . . . with skeletal fluoride levels less than 0.4-0.5% bone ash." We do not think that this threshold is likely to be approached from fluoridated drinking water or fluoride-supplemented dentifrices. We found the mean skeletal fluoride to be only 0.1% bone ash at baseline in our patients with postmenopausal osteoporosis who had long-term exposure to fluoridated water.

We agree that measurement of bone quality in iliac crest biopsies may not be reflective of bone strength at other skeletal sites; biopsies at other sites are not feasible because of bioethical constraints. However, we take exception to Dr. Turner's claim that our ultrasound measurements in fluoridic bone may not accurately reflect bone strength. As he agrees, the ultrasound measurement describes elasticity; a strong correlation between elasticity and breaking strength has been reported not only in untreated but also in fluoride-treated bone. We also recognize that bone size

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