

## EDITORIAL



## Strontium Ranelate — A Novel Therapy for Osteoporosis or a Permutation of the Same?

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Osteoporosis was originally described in literature and art hundreds of years ago. Our ability to treat this disease lay dormant for centuries, but in the past 10 years, clinical trials have improved treatment options and efficacy. In this issue of the *Journal*, Meunier et al.<sup>1</sup> report on their study of the safety and effectiveness of strontium ranelate as a putative, novel therapy for osteoporosis.

Strontium was originally detected in lead mines near Strontian, Scotland, in the late 1700s. This earth element is present in water and food and in trace amounts throughout the skeleton. Although absorption is poor when strontium is consumed orally, calcified tissues and areas of active osteogenesis take up 50 to 80 percent of the absorbed dose; excretion is largely renal. The uptake of strontium by bone seems to occur mostly by ionic substitution at low rates at the crystal surfaces of the bone matrix, without affecting mineral structure.<sup>2</sup> Because of its bone-seeking properties, strontium was used widely in the 1950s for the management of osteoporosis,<sup>3</sup> and more recently, the beta emitter strontium-89 was used for painful, malignant bone diseases. Strontium fell out of favor as a treatment for osteoporosis decades ago because mineralization defects were observed and the synthesis of calcitriol was inhibited.<sup>3</sup> These adverse effects were thought possibly to have been due to calcium-deficient diets and the doses used, and there has recently been renewed interest in developing this old element as a new compound, strontium ranelate.<sup>4</sup>

In contrast to other known therapies for osteoporosis, strontium ranelate appears to induce uncoupling in bone remodeling, stimulating bone formation and reducing resorption in normal bone in rats, mice, and adult monkeys.<sup>4</sup> Similar effects

were observed in rodent models of osteoporosis that was induced by immobilization and estrogen deprivation.<sup>5,6</sup> No mineralization defects were recorded in these animal models with prolonged exposure to strontium ranelate at doses of up to 1800 mg per kilogram of body weight per day.<sup>2,4-7</sup> The precise cellular mechanism through which strontium ranelate may act as an uncoupling agent is unknown, although the induction of cellular differentiation<sup>4</sup> and the activation of the calcium-sensing receptor<sup>8</sup> have been suggested as contributing factors. Years before the calcium-sensing receptor was cloned, strontium was shown to suppress the release of parathyroid hormone. More recently, it has been shown to activate the calcium-sensing receptor in other cell systems.<sup>8</sup> Whether the calcium-sensing receptor also mediates some of the effects of strontium on bone, as it reportedly does for calcium, remains to be determined.<sup>8</sup>

The promising preclinical data on strontium ranelate led to four major trials in the mid-1990s.<sup>1,9-11</sup> In two dose-ranging trials involving more than 500 women over a two-year period, strontium ranelate increased adjusted bone mineral density of the lumbar spine in a dose-dependent manner.<sup>9,10</sup> (On dual-energy x-ray absorptiometry, a metal with an atomic number greater than that of calcium, such as strontium, will weaken the penetration of x-rays and therefore result in an overestimation of measured bone mineral density and content. Formulas have been derived to correct for the artificial elevation observed in the measured bone mineral density for the spine but not for the hip.<sup>1</sup>) The results of these two studies led to the current three-year, double-blind, placebo-controlled trial conducted by Meunier et al., who tested the safety and efficacy of

2 g of strontium ranelate per day in reducing vertebral fractures in postmenopausal women with established osteoporosis.<sup>1</sup>

Patients underwent randomization after a run-in period of 2 to 24 weeks of calcium and vitamin D supplementation. The intention-to-treat analyses were based on 1442 women for whom radiographs were obtained after randomization. At three years, bone mineral density at the spine, adjusted for the strontium content of the bone, showed an increase of 6.8 percent over base line. There was a 40 to 50 percent reduction in the rate of morphometric and symptomatic vertebral fractures at one and three years in the strontium ranelate group as compared with the placebo group. There was no effect on peripheral fractures, and the study was not designed to address that issue. The overall rate of adverse events in the strontium ranelate group was similar to that in the placebo group as well as to the rates in other studies.<sup>9,10</sup> The incidence of diarrhea was 6 percent in the strontium ranelate group, which was higher than the incidence in the placebo group.<sup>1</sup> There was a small and transient rise in serum creatine phosphokinase concentrations, which was of no obvious clinical consequence, and there was no change in vitamin D metabolites.<sup>1</sup>

In 2000, the World Medical Association issued the revised Declaration of Helsinki, condemning the use of placebo in studies when established therapies are available,<sup>12</sup> which raises the question of whether use of a placebo in this trial was acceptable. The American Society for Bone and Mineral Research sponsored two conferences, in 2001 and 2002, to debate this complex issue, a discussion that is beyond the scope of this editorial.<sup>13</sup> However, specific points should be made about this particular strontium ranelate trial. It was initiated in 1996, well before the World Medical Association's recommendation, at a time when efficacious treatments for osteoporosis were scarce.<sup>1</sup> The World Medical Association has since issued a "clarification," justifying the use of placebo when compelling and scientifically sound methodologic reasons necessitate it.<sup>12</sup> In the case of strontium, use of a placebo can be justified on this basis.

The 40 to 50 percent reduction in the risk of vertebral fractures reported in this trial is similar to the reduction reported with antiresorptive drugs and slightly lower than the reduction with parathyroid hormone, a bone-forming drug.<sup>1</sup> Bone mineral density is an excellent predictor of bone strength and the risk of fracture. A 2-g dose of strontium

ranelate was presumably chosen because it resulted in the largest changes in adjusted bone mineral density in the lumbar spine.<sup>10</sup> We have since learned that changes in bone mineral density in response to antiresorptive therapy account for only a small proportion of the reduction in the risk of fractures.<sup>14</sup> Although there is no clear evidence that the same observation applies to strontium, an examination of the data suggests that it may. Indeed, despite differences in the adjusted bone mineral density of the spine, a 50 percent reduction in the risk of fracture has been reported in patients who were given strontium ranelate orally at doses of 0.5 and 2 g per day, but not in patients given 1 g.<sup>10</sup> Similarly, in the current trial, the reduction in the risk of fractures was 50 percent at one year and 40 percent at three years, despite changes in measured bone mineral density between the two time points.<sup>1</sup>

These observations lead to the intriguing possibility that lower doses of strontium ranelate might have been as effective in reducing the risk of vertebral fractures. The efficacy of strontium ranelate in reducing the risk of nonvertebral fractures, at a dose of 2 g a day, is currently under evaluation in a trial involving more than 5000 elderly women. Preliminary analyses show a 16 percent reduction in the risk of peripheral fractures ( $P=0.05$ ) and a 41 percent reduction in the risk of hip fractures ( $P=0.025$ ).<sup>11</sup>

An evaluation of the metabolic profile of bone may shed light on the dual mechanism of action of strontium ranelate that has been proposed. Values for serum bone-specific alkaline phosphatase, an index of bone formation, increased steadily and peaked at 20 percent above base-line values at two years, whereas the response of serum C-telopeptide cross-links, an index of bone resorption, was biphasic, with concentrations that were 5 percent above base-line values at two years.<sup>1</sup> The stimulatory effect of strontium on alkaline phosphatase is consistent among studies, but the suppression of bone resorption is minimal and less predictable.<sup>1,9,10</sup> The magnitude of the changes in these biochemical markers is modest at best, as compared with the changes reported with antiresorptive therapy, bone-formation therapy, or a combination of the two.<sup>1,15</sup>

Bone histomorphometry, a powerful tool in assessing the safety and mechanism of action of drugs in osteoporosis, was performed on 14 samples in this trial, and the authors summarized the findings as showing that there were no mineralization defects.<sup>1</sup> These results are similar to previous observations in 64 subjects.<sup>10</sup> However, details on in-

dexes of bone formation and resorption were not provided in either study.<sup>1,10</sup> The mechanism of action of strontium ranelate on bone seems to be complex, is possibly dose- and time-dependent, and will unfold once details of the histomorphometric indexes become available.<sup>1,10</sup>

The calcium-sensing receptor, a divalent cation receptor, regulates many essential physiologic functions, including hormone secretion, gene expression, ion channels, chemotaxis of cells, proliferation and differentiation of cells, and cell apoptosis.<sup>8</sup> The concentrations of strontium ranelate that are known to activate the calcium-sensing receptor *in vitro* were reported to be at least 0.4 mmol per liter,<sup>8</sup> whereas the median serum level of strontium ranelate in the trial by Meunier et al. had reached a plateau at 0.12 mmol per liter at three months.<sup>1</sup> Because neither the timing of the blood collection (whether blood samples were obtained at a time of peak or trough levels) nor the spread of the values above the median was specified, the effect of such values on the calcium-sensing receptor is unclear. Serum parathyroid hormone levels decreased slightly, in parallel with a decrease in serum levels of calcium and an increase in serum levels of phosphate, an observation that is consistent with activation of the calcium-sensing receptor at the level of the parathyroid gland.<sup>1</sup> Conversely, calcitonin levels did not change.<sup>1</sup> Whether the serum levels of strontium achieved with the dose of 2 g a day could induce activation of the calcium-sensing receptor in other tissues or activation of calcium-sensitive pathways that are independent of the calcium-sensing receptor is unclear and warrants evaluation, particularly in patients with impaired renal excretion. Such patients were, however, justifiably excluded from these trials.<sup>1,9,10</sup>

The current trial establishes the efficacy of strontium ranelate, a familiar element relaunched as a new compound, in reducing the risk of vertebral fractures and its role in the armamentarium of therapies for osteoporosis. New forms of technology and insights pertaining to the determinants of bone quality will be invaluable in the long-term monitor-

ing of the safety and efficacy of this new compound, as well as of others, and will elucidate the mechanisms behind its molecular effects on bone.

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