**Characteristics of strontium**

Strontium was discovered in 1790 in a mine close to the Scottish village Strontian and was isolated in 1808. Strontium is one of the alkaline earth metals and is never found in its free form in nature because it easily oxidises, forming strontium oxide. Strontium, along with calcium and magnesium, belongs to group 2 of the periodic table which are divalent cations, which, in biological liquids can have different degrees of bonds with blood proteins. The binding to proteins of strontium is in the same order of magnitude as that of calcium. In the human body there are only traces of strontium. A normal diet supplies from 2 to 4 mg of strontium per day, although the quantity can be higher if the diet is rich in cereals or vegetables.

Given the similarity in the behaviour of both elements, the radioisotopes of strontium have been used for kinetic studies of the metabolism of calcium. However, there are important biological differences between them, which are in part explained by the greater molecular weight of strontium. Common transportation pathways have been described, for example strontium competes with calcium in intestinal absorption and in renal tubular reabsorption. Strontium is absorbed less than calcium, this difference in the intestinal tract could be due, in part, to the smaller size of the calcium atom. On the other hand, the renal clearance of strontium is nearly three times greater than that of calcium, perhaps due to a greater secondary tubular absorption because of the larger size of the strontium atom.

**Relationship of strontium with bone**

The quantity of strontium in the skeleton is very small, and represents only 0.035% of the content of calcium. After its administration it is deposited almost exclusively in bone. Like sodium and lead, strontium can substitute for calcium in the position which it occupies in hydroxyapatite.

In 1952, Shorr and Carter demonstrated that the addition of a moderate quantity of strontium lactate improves the deposition of calcium in the bone. One can say that this observation was the first suggestion in the literature that strontium could be useful in the treatment of alterations in bone metabolism. In 1959, McCaslin showed in a small study that in patients with osteoporosis strontium lactate reduced bone pain, at the same time as improving the X-ray images of demineralisation. However, these observations did not awaken great interest in the researchers of that time, probably due to the mineralisation defects which a high dose of strontium was known to produce.

Subsequently, in the 90s, from the study of Marie et al., various researchers confirmed progressively and uniformly, that strontium ranelate reduced bone resorption, maintaining formation and increasing bone volume without inducing mineralisation defects.

**The effect of strontium ranelate on markers for bone formation and resorption**

Anti-resorptive and anti-catabolic drugs prevent the destruction of bone by reducing the rate of...
bone remodelling, as is reflected in the decrease in markers for bone resorption and formation. The bone formation drugs such as teriparatide and PTH 1-84, increase bone formation and secondarily, an increase in bone resorption is observed\(^8\). However, the action mechanism of strontium ranelate is different to that of other drugs; in fact, by its action in opposing resorption and formation, it has been classified within a new group: dual action\(^2\)\(^\text{1}^\text{1}\), Figure 1.

One of the studies (randomised, double blind, of 3 years duration)\(^2\)\(^\text{2}\) which was carried out, for the registration of the drug, in 1649 postmenopausal women with osteoporosis and at least one vertebral fracture, after 3 months of treatment, found in the group taking strontium ranelate an increase in bone-specific alkaline phosphatase and a decrease in C-telopeptide, compared with the placebo group. These changes, although more pronounced during the first six months of treatment, persisted throughout the study, remaining statistically significantly different from the placebo group during the three years of the study.

**Target molecules for strontium ranelate**

There is no doubt as to the clinical efficacy of this drug which, thanks to the careful design of the studies for its registration (SOTI and TROPOS)\(^2\)\(^\text{3}\), has shown long term (5 years) beneficial effects on vertebral and non-vertebral fractures compared with a placebo\(^2\)\(^\text{4}\)\(^\text{5}\). However, there remain doubts over the molecular signalling mechanisms which come to produce the observed effects on osteoblasts, osteocytes, osteoclasts and definitively on bone metabolism.

The similarities of strontium with calcium, already mentioned at the start of this review\(^2\)\(^\text{6}\), have generated many studies intended to investigate if the final action mechanism of strontium shares signalling pathways with calcium, involving the receptor-sensor of calcium (CaSR) in these responses\(^2\)\(^\text{7}\). *In vitro* studies show that strontium activates CaSR\(^2\)\(^\text{8}\)\(^\text{9}\), in turn it has been shown that CaSR is implicated in the replication of pre-osteoblasts and osteoblasts induced by strontium ranelate\(^2\)\(^\text{10}\)\(^\text{11}\).

However, the activation of CaSR is not the only mechanism which has been implicated in the signalling pathways of strontium. Other parallel mechanisms could exist through the cation receptor-sensors, similar to CaSR\(^2\)\(^\text{12}\). Among the activated pathways are found protein kinase C, protein kinase D and p38, signals involved in cellular replication induced by strontium ranelate\(^2\)\(^\text{13}\).

Recent data obtained in cultures of human primary osteoblasts stimulated with strontium ranelate have strengthened the idea of the involvement of CaSR in the molecular signalling pathways of this drug\(^2\)\(^\text{14}\)\(^\text{15}\). Strontium ranelate has shown itself to be capable of increasing the levels of ARNm and of the protein of osteoprotegerin (OPG), in turn suppressing RANKL (receptor activator of NF-κB ligand). In addition, strontium ranelate also stimulates osteoblast replication and differentiation, increasing cellular survival under stress. These positive effects of strontium ranelate are suppressed when CaSR is partially silenced, suggesting the significant involvement of CaSR in these responses\(^2\)\(^\text{16}\).

**General effects of strontium in experimental models**

The action mechanism of strontium ranelate is based on its capacity to increase the formation, and reduce the resorption, of bone simultaneously, but to a moderate extent, restabilising the balance between the two processes in the same way as that observed in women before the menopause. This dual action mechanism also has positive effects on bone resistance\(^2\)\(^\text{17}\)\(^\text{18}\)\(^\text{19}\).

The preclinical development of strontium ranelate included numerous *in vitro* and *in vivo* studies, with experimental models\(^2\)\(^\text{20}\)\(^\text{21}\). The results have been consistent and reproducible and, very importantly, the concentration of strontium ranelate used in most of the experimental studies has been within similar ranges as those used in patients.

In normal female rats, strontium ranelate increases bone formation and reduces bone resorption, resulting in an increase in bone mass at the same time as conserving of bone mineralisation\(^2\)\(^\text{22}\)\(^\text{23}\). In addition, in both normal male and female rats, treated with strontium over prolonged periods, an increase in the parameters of bone formation and a decrease in the parameters of bone resorption is observed\(^2\)\(^\text{24}\).

In ovariectomised rats treatment with strontium reduces the number of osteoclasts and the osteoclastic surface, whilst increasing the osteoblastic surface and the rate of bone formation with a magnitude of response similar to that obtained by administering oestrogens. This effect of strontium succeeds in preventing the loss of bone mass in both femur and vertebrae\(^2\)\(^\text{25}\). Also, in immobilisation models, when bone resorption is high and formation low, strontium ranelate has been successful in correcting both effects and in conserving bone mass\(^2\)\(^\text{26}\).

In spleen cells and in murine primary osteoblasts and osteoclasts derived from cranial vault, strontium ranelate has been capable of stimulating

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*Figure 1. Classification of different drugs for the treatment of osteoporosis by function of their effects on remodelled bone*
the formation of osteoblasts and inhibiting osteoclast formation, independently of the degree of proliferation and differentiation in which the cells are found\textsuperscript{36}.

**Specific effects of strontium on osteoblastic proliferation and osteocytes**

*In vitro*, strontium ranelate has been shown to exert a positive effect on the replication of osteoprogenitor cells and pre-osteoblasts at the same time as it increases the syntheses of collagen and non-collagen proteins in cells from the cranial vault and in mature osteoblasts in rats\textsuperscript{37}. In addition, strontium ranelate stimulates the differentiation of osteoblastic precursors or mature osteoblasts capable of intervening in bone mineralisation. Strontium ranelate has also been capable of increasing the expression of critical genes in osteoblastic differentiation, such as Runx 2 and BSP (bone sialoprotein)\textsuperscript{32}. On the other hand, it has not shown any effect on the gene for osteocalcine, the protein implicated in the regulation of the osteoid matrix. The effects of strontium ranelate are not equal in all the cell lines studied, its impact on gene expression varies according to the cell type, as has been demonstrated with pre-osteoblasts U-33 or in mature osteoblasts OB-6. In general, strontium ranelate has always been more efficacious at the level both of the cellular response and of mineralisation (measured by Von-Kossa), in less differentiated cells. Therefore, one of its important properties appears to be its capacity to stimulate osteoblastic differentiation. In summary, the association and sum total of the effects of strontium ranelate on preosteoblasts and osteoblasts, and their beneficial consequences on mineralisation, explain in great measure the positive action of the drug on bone formation.

At the present time there is a growing interest in the role which the osteocytes play in the health of bone, and their potential as therapeutic targets\textsuperscript{30}. The osteocytes are not inactive residual cells, resulting from active osteoblasts trapped in newly-formed bone, but play an important role in structural remodelling. They are responsible for the initiation of bone repair in response to micro-cracks\textsuperscript{34}, and for the formation of new bone in response to an increase in load\textsuperscript{35}. The reduced density of osteocytes has been associated with osteoporotic fractures\textsuperscript{8}, and it has been speculated that if the osteocytes have a mechanico-sensory function, their decrease could imply a lower capacity to detect micro-lesions in the bone matrix, and as a consequence result in a higher accumulation of micro-lesions and material fatigue with age\textsuperscript{35}. Strontium ranelate has shown itself capable of favouring the differentiation of human osteoblasts to osteocytes. In cultures, in conditions of mineralisation, treatment with strontium ranelate increases, dose and time dependently, osteoblastic replication, inducing a phenotype similar to the osteocyte and increasing the expression of alkaline phosphatase, of STRO-1, of ARNm of the matrix protein of dentin and of sclerostin, markers which support the existence of a phenotypic change to osteocyte\textsuperscript{36}. Figure 2.

![Diagram of regulation pathways of strontium ranelate on bone](image)

**Specific effects of strontium on osteoclasts and bone resorption**

The positive effects of strontium ranelate on bone metabolism does not only depend on its effect as a stimulator of bone formation, but also on its capacity to reduce bone resorption.

Given the known effect of oestrogen deficiency on the increase in bone resorption and as a consequence, in the loss of a neutral balance between bone formation and resorption, oestrogen deprivation in rats has been the model most commonly used to study the effects of anti-osteoporotic drugs. Strontium ranelate has shown in histomorphometric studies to reduce bone resorption (number of osteoclasts and osteclastic surface) with final results similar to those observed in rats in which ovariectomy has not been carried out\textsuperscript{38}.

The inhibition of bone resorption obtained with strontium ranelate could be explained through the inhibition of both the differentiation of the osteoclasts and their capacity for resorption. In rat osteoclast cultures strontium inhibits, in a dose-dependent way, in previously stimulated osteoclasts, the expression of carbonic anhydrase II and the receptor for vitronectin. This resorption inhibitor effect increases when the incubation is prolonged\textsuperscript{38}.

As has already been commented on, there are data which indicate that strontium ranelate could also have the effect of stimulating the production of OPG, a known inhibitor of osteoclastogenesis\textsuperscript{39}. Primary cultures of adult human osteoblasts trea-
ted with strontium ranelate under conditions of mineralisation showed a time dependent increase in the expression of ARNm of OPG. The effect of strontium ranelate on the expression of RANKL and its action on the osteoblasts.25. Strontium ranelate could have an inhibitory effect on osteoclastic differentiation fundamentally through its action on the osteoblasts.25

Summary
It is 50 years since it was suggested for the first time that strontium could have a positive effect on bone metabolism, improving the incorporation of calcium in the bone.1 However, it was the start of the 90s, with the initiation of studies with strontium ranelate, when the real knowledge of its biological and clinical effects began.

The efficacy of strontium ranelate in the treatment of postmenopausal osteoporosis has been widely proven: for vertebral and non-vertebral fractures, in all age ranges and in the presence of all risk factors for osteoporosis.12,33,34,40-43. The result of its administration is an increase in bone formation and a reduction in bone resorption, both moderate, in an almost physiological range, equal to that of calcium. The effect on remodelled bone results in increases in bone mass, an increase in bone resistance and, as a final result, a reduction in the risk of fractures.

The final, close up action mechanism seems clearly to involve CaSR (in its effect as a modulator of osteoclastogenesis) and other cation sensors (which are to be found in the different maturation of osteoblasts) which seem to be crucial in the molecular signalling pathways of this drug. This will bring a higher capacity for bone synthesis and mineralisation, with a positive balance in each remodelling cycle, with the end result of an improvement in bone resistance.

Bibliography


