


**Tania Winzenberg**

MBBS, FRACGP, MMedSc(ClinEpi), PhD, is Research Fellow – General Practice, Menzies Research Institute, University of Tasmania. [tania.winzenberg@utas.edu.au](mailto:tania.winzenberg@utas.edu.au)

**Sandi Powell**

MBBS(Hons), is junior Research Fellow, Menzies Research Institute, and senior endocrinology registrar, Royal Hobart Hospital, Tasmania

**Graeme Jones**

MBBS(Hons), FRACP, MMedSc, MD, FAFPHM, is Head, Musculoskeletal Unit, Menzies Research Institute, Tasmania.

# Strontium ranelate

## Does it affect the management of postmenopausal osteoporosis?

This series of articles facilitated by the Cochrane Musculoskeletal Group (CMSG) aims to place the findings of recent Cochrane musculoskeletal reviews in a context immediately relevant to general practitioners. This article considers whether the availability of strontium ranelate affects the management of postmenopausal osteoporosis.

**Osteoporosis is a costly condition<sup>1,2</sup> and is the fifth most common musculoskeletal problem managed in general practice at 0.9 per 100 patient encounters.<sup>3</sup> Secondary prevention of osteoporotic fracture is poorly implemented<sup>4</sup> despite the availability of efficacious treatments.**

Strontium ranelate, a pharmacological treatment for osteoporosis which is relatively new to Australia, has been available on the Pharmaceutical Benefits Scheme (PBS) by authority prescription since April 2007.<sup>5</sup> Strontium is

the pharmacologically active component of the compound and has been shown to simultaneously decrease bone resorption and stimulate bone formation both in vitro and in animal models,<sup>6</sup> although the exact mechanisms for these actions are as yet unclear.

O'Donnell et al<sup>1</sup> performed a systematic review to assess the efficacy and adverse effects of strontium compared to either placebo or other treatments for postmenopausal osteoporosis. The review results are summarised in *Table 1* and how these results might affect practice are shown in *Table 2*.

**Table 1. Key review results<sup>1</sup>**

- The review included four randomised controlled trials (RCTs) three of which were termed treatment populations, with a mean lumbar spine T-score  $<-2.5$ .<sup>7-9</sup> In two of these, all participants had sustained a previous vertebral fracture,<sup>7,8</sup> and in one, around 55% had sustained either vertebral or nonvertebral fracture.<sup>9</sup> The fourth study was in early postmenopausal women with T-score  $<-2.5$  and no fracture<sup>10</sup> (termed a prevention population)
- All participants in the studies in treatment populations received both calcium and vitamin D supplementation
- 2 g of strontium ranelate given daily for 3 years in a treatment population<sup>1</sup> resulted in a 37% reduction in vertebral fractures (RR: 0.63, 95% CI: 0.56, 0.71) and a 14% reduction in nonvertebral fractures (RR: 0.86, 95% CI: 0.75, 0.98). The number needed to treat (NNT) to prevent one vertebral fracture over 3 years was 13, and to prevent one nonvertebral fracture, 58
- The NNT to prevent one vertebral fracture over 1 year was 32
- In the single study<sup>9</sup> measuring hip fracture outcomes separately, after 3 years there was a 15% decrease in risk of hip fracture which was not statistically significant (RR: 0.85, 95% CI: 0.61–1.19) in the full study sample (n=4932), and a decrease of 36% (RR: 0.64, 95% CI: 0.41–0.99) in a subgroup (n=1977) at high risk of hip fracture defined by age  $>74$  years of age and a femoral neck bone mineral density (BMD) T-score  $<-3$ . Hip fracture was not the primary outcome for this study, and the study was not designed with sufficient power to examine hip fracture separately. Thus strontium's effect at the hip remains unclear
- There were no fracture outcomes measured in the prevention population, although strontium ranelate at a lower dose (1 g/day) than that which reduced fracture risk increased BMD, adjusted for strontium content of bone, at the lumbar spine by 1.4%. The increase at the femoral neck was 2.5% but this was not adjusted for strontium content of bone
- Strontium ranelate did not cause gastritis, back pain or death, but six out of 100 women taking strontium ranelate experienced diarrhoea compared to four out of 100 taking placebo, with a number needed to harm of 56
- The risk of vascular system disorders including venous thromboembolism (two trials, n=6669, 2.2 vs. 1.5%, OR: 1.5, 95% CI: 1.1–2.1) and pulmonary embolism (two trials, n=6669, 0.8 vs. 0.4%, OR: 1.7, 95% CI: 1.0–3.1) as well as nervous system disorders such as headache (3.9 vs. 2.9%), seizures (0.3 vs. 0.1%), memory loss (2.4 vs. 1.9%) and disturbance in consciousness (2.5 vs. 2.0%) is slightly increased with taking 2 g of strontium ranelate daily over 3–4 years
- There were no RCTs identified which compared strontium ranelate to other treatments of postmenopausal osteoporosis

## Conclusion

Strontium ranelate has demonstrated efficacy for the prevention of vertebral and nonvertebral osteoporotic fracture in postmenopausal women who have previously sustained an osteoporotic fracture or have a BMD  $-2.5$ , although its effect on hip fracture risk is less certain. In the absence of

head-to-head RCTs it is not possible to comment on the relative efficacy of strontium compared to other treatments such as bisphosphonates, raloxifene and parathyroid hormone. However, its efficacy and safety suggests that it could be considered a first line treatment for postmenopausal osteoporosis and may be particularly useful

where bisphosphonates are contraindicated or not tolerated. There is potential for strontium ranelate to play a role in the prevention of postmenopausal bone loss as it has been shown to increase BMD in this population,<sup>10</sup> and posthoc analyses have shown decreased fracture risk in osteopenic postmenopausal women without fractures.<sup>14</sup> However, more data are required to confirm this. Further research is also needed to determine whether the efficacy of strontium ranelate is affected by previous bisphosphonate use.

Conflict of interest: GJ sits or has sat on advisory boards for MSD (alendronate), Roche (ibandronate) and Servier (strontium). These companies had no input into the writing of this paper.

### Table 2. Putting evidence into practice

#### Case study 1

Mrs Casey, 68 years of age, has been generally well and leads an active lifestyle with regular bushwalking. She recently sustained a Colles' fracture when she slipped on a frosty path. Both you and Mrs Casey are concerned about the possibility of osteoporosis. A dual energy X-ray absorptiometry (DEXA) scan showed that her lumbar spine T-score was in the osteoporotic range at  $-2.8$ . She wants to discuss her treatment options with you.

Mrs Casey has no contraindications to any of the PBS listed treatments for osteoporosis. You explain that bisphosphonates, specifically alendronate and risedronate, are recommended as first line treatment to prevent subsequent osteoporotic fracture because of the strength of evidence for their effectiveness at preventing both vertebral and nonvertebral fractures in this situation.<sup>11</sup> You explain that an added advantage is that they can be taken once per week which reduces the gastrointestinal side effects and makes them easier to take. You mention that there are other treatments, the main options being:

- strontium ranelate, which is a relatively new drug which has to be taken daily. While this review has shown its effectiveness at reducing vertebral and nonvertebral fractures, there have been no head-to-head studies with bisphosphonates, so you cannot directly compare it with these first line drugs. However, the magnitude of benefit in terms of fracture reduction is similar. While it has been studied in approximately 10 000 women for up to 5 years, it has not yet been widely used, thus, there may be as yet unknown side effects associated with its use<sup>11</sup> as has recently been shown for bisphosphonates and osteonecrosis of the jaw.<sup>12</sup> Despite this, the evidence suggests this should also be considered as a first line treatment
- raloxifene, but this only decreases the risk of vertebral fractures not other fractures and is considered a second line treatment<sup>11</sup>
- parathyroid hormone increases bone density substantially and decreases both vertebral and nonvertebral fractures substantially. It has been used in over 100 000 women worldwide. However, it requires daily injections under the skin, is not listed on the PBS and costs \$16 000 per 18 month course. It is generally used for severe osteoporosis or when other agents are unsuitable.<sup>11</sup>

You recommend the use of a bisphosphonate to start with, and Mrs Casey is happy with this recommendation.

#### Case study 2

Mrs Yusef, 82 years of age, has been discharged from hospital after a fractured neck of femur. In hospital she was commenced on alendronate to treat her osteoporosis and prevent further fracture. While Mrs Yusef is physically reasonably well, you are aware that there are some issues with her memory, which have been brought to your attention by her husband. Today her husband comes in concerned because he is finding it increasingly difficult to ensure that his wife stays upright for the 30 minutes necessary after her weekly dose is taken, and she is complaining about indigestion after taking the alendronate.

What do you do?

Mrs Yusef's inability to stay upright for the 30 minutes necessary after drug administration is a contraindication to her use of oral bisphosphonates. Strontium ranelate (2 g of granules mixed in water) is taken at bed time, 2 hours after food with no other special instructions and is effective at reducing both vertebral and nonvertebral fractures. You decide that in this situation, strontium ranelate is the simplest alternative treatment to try first, especially as it is the only agent which has been shown to prevent fractures in those over 80 years of age.<sup>13</sup>

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**afp** CORRESPONDENCE email: [afp@racgp.org.au](mailto:afp@racgp.org.au)