

CLINICAL PRACTICE

The safety of osteoporosis medication

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Osteoporosis is a common, costly and serious disease, which is still too often regarded as an inevitable part of the normal ageing process and therefore sub-optimally treated, especially in the elderly – in fact, only two out of every 10 patients who sustain a hip fracture receive any form of assessment or prophylactic therapy for osteoporosis. One out of five patients die within 1 year after a hip fracture, and <50% are capable of leading an independent life. Yet very effective anti-fracture therapy, capable of reducing fracture risk by 35 - 60%, is available. A number of publications have recently questioned the safety of drugs routinely used to treat patients with osteoporosis. This paper attempts to put the situation into perspective and expresses the National Osteoporosis Foundation of South Africa's view on the safety of these drugs. Their efficacy in preventing skeletal fractures and their cost-effectiveness are not addressed in any detail. The paper emphasises the fact that all osteoporosis medications have side-effects, some of which are potentially life-threatening.

S Afr Med J 2014;104(4):279-282. DOI:10.7196/SAMJ.7505



Conventionally, osteoporosis medication is classified into anti-resorptive drugs, anabolic agents or stimulators of bone formation, and agents with a dual or complex action on bone.

Anti-resorptive agents Calcium and vitamin D

Treatment of osteoporosis with calcium and vitamin D only is associated with a modest reduction in fracture risk, and calcium with or without vitamin D has also been a mandatory component in all drug trials assessing the anti-fracture efficacy of potent bone-active drugs. Calcium and vitamin D have generally been regarded as safe and largely without side-effects when used in their recommended doses – supplemented as approximately 600 mg elemental calcium per day (to ensure a total daily intake of about 1 000 mg per day) and 800 - 1 200 IU vitamin D per day. Higher doses of vitamin D may be used in pregnancy and lactation, and to treat proven osteomalacia.

Constipation is not uncommon in patients on calcium supplements, especially when calcium carbonate is used, and this is an important cause of poor drug adherence. An increased risk of renal stones (10 - 15%) has been reported, but there is a paucity of controlled or prospective data. Hypercalcaemia generally only occurs when high and prolonged doses of vitamin D or one of its active metabolites (not recommended for routine osteoporosis treatment) are used.

Bolland *et al.*^[2] recently published a meta-analysis suggesting that high-dose calcium supplementation in postmenopausal women with osteoporosis is associated with an increased risk of cardiovascular disease (CVD). On further scrutiny of the paper it is, however, quite clear that the increased risk of CVD was only evident in subjects who consumed at least 800 mg calcium per day in their diet, in addition to the high-dose supplementation. Furthermore, results of the recently published Canadian Multicentre Osteoporosis Study, which involved 10-year longitudinal follow-up of over 9 000 participants, showed that calcium supplementation of up to 1 000 mg per day was associated with no harm, and in fact with reduced mortality, in women.^[3]

It is therefore fair to conclude that:

- Whenever possible, an adequate dietary intake of calcium is preferable to supplementation.
- Calcium should not be supplemented in those with an adequate dietary intake.
- When used in recommended doses to prevent/treat osteoporosis, calcium and vitamin D are safe.
- Care should be taken when considering supplementing patients with established CVD or impaired renal function.

Menopausal hormone therapy

Menopausal hormone (oestrogen with or without progestin) therapy (MHT) has been convincingly shown to increase bone mineral density (BMD) and to reduce clinical fracture risk at all sites (including the spine and hip), not only in subjects at high risk of sustaining an osteoporotic fracture, but specifically in those with a near-normal BMD and no prior fracture. This was suggested by numerous observational studies, conclusively proven by the Women's Health Initiative (WHI),^[4] and further corroborated by the large National Osteoporosis Risk Assessment (NORA)^[5] and Million Women Studies.^[6]

Initial results from the WHI, however, suggested that MHT was associated with an increased risk of CVD, thrombo-embolic disease (TED), stroke and breast cancer.^[7] These agents have therefore largely been abandoned as first-line treatment for osteoporosis by most regulatory authorities. Objections to the conclusions drawn from the WHI have again been highlighted recently^[8] and include:

- Incorrect or inappropriate study design (e.g. heavy emphasis was placed on a single, unvalidated tool to assess the safety of MHT, the so-called 'global index').
- Poor data analysis (e.g. lack of distinction between nominal and adjusted risk, and emphasis on relative as opposed to absolute risk – e.g. emphasising the 2-fold increase in TED that accompanies the use of MHT, yet omitting the fact that the absolute risk increases from 1 in 1 000 postmenopausal women to 2 in 1 000 women).
- Disregard for the high rates of discontinuation in the active treatment arm (42%) and crossover to active treatment in the placebo arm (11%).

- Extrapolation of data obtained in 64-year-old subjects (the average age of women included in the WHI) to young 50-year-old individuals – stratification of especially CVD according to age/time since menopause has subsequently been shown to be critical.
- Inadequate differentiation between data obtained from the oestrogen-only and the oestrogen-plus-progestin study arms – e.g. available evidence suggests that the increased risk of breast cancer associated with the use of MHT is entirely limited to the use of oestrogen plus progestin, and does not apply to the use of oestrogen-only therapy.
- Generalisation about the specific progestin used in combined hormone therapy.
- Disregard for the protective role of transdermal MHT on the development of the metabolic syndrome and its associated vascular complications.

A detailed discussion of this debate is beyond the scope of this paper. Suffice to reiterate the recommendations of the National Osteoporosis Foundation of South Africa (NOFSA) guidelines, published in 2010,^[11] namely:

- MHT should only be initiated for specific indications in subjects without contraindications to its use (e.g. current breast cancer, undiagnosed genital bleeding, current deep-vein thrombosis, untreated hypertension/CVD).
- In the absence of contraindications, the use of MHT in women aged 50 - 60 years is safe and appropriate to manage osteoporosis – in fact, in individuals with menopausal symptoms it should be regarded as the drug of choice.
- It is best not to initiate MHT after age 60 years for the sake of skeletal protection only; continued use of MHT after age 60 may, however, be considered if other treatment options are contraindicated.
- If fracture protection is sought, doses of hormone therapy known to provide fracture protection (i.e. 0.625 mg/day conjugated equine oestrogen or equivalent) should be used. Low-dose hormone therapy has been shown to protect against loss of BMD, but fracture data are still awaited.
- A reduction in BMD may occur once MHT is discontinued, and treatment with another bone-active drug should therefore be considered at that stage.

Calcitonin

Calcitonin was previously reserved for individuals who could not tolerate more effective therapy (e.g. with a creatinine clearance rate <30 ml/min).^[11] Up to a third of patients experienced nausea, diarrhoea and flushing. Calcitonin has recently been associated with a 1 - 3% increase in the risk of systemic malignancies and has therefore been withdrawn from the market as a useful and safe agent to treat osteoporosis.^[9]

Bisphosphonates

The bisphosphonates (BPs) are universally regarded as a first-line treatment for osteoporosis in postmenopausal and elderly women, in men, and in a number of secondary osteoporoses, including glucocorticoid-induced osteoporosis.

Oral BPs may cause an erosive oesophagitis (especially if taken incorrectly) with nausea, heartburn, chest pain and vomiting. The intravenous BPs may precipitate acute renal failure (when rapidly injected) and have been associated with a severe flu-like syndrome (usually a first-dose, acute-phase reaction that responds to paracetamol or non-steroidal anti-inflammatory drugs), hypocalcaemia (especially in the presence of vitamin D deficiency),

or diffuse bone pains. Skeletal retention of BPs is very long (terminal half-life >10 years) and, under certain circumstances, even lifelong. Concerns regarding fetal safety have therefore been expressed where women of child-bearing age have been subjected to many years of BP treatment. No conclusive data that BPs are harmful to the fetus have been forthcoming, but clinicians should be alerted regarding unnecessary and unproven treatment with BPs of younger women with isolated, modest decreases in BMD. Initial concerns about oesophageal cancer with oral BPs and atrial fibrillation with intravenous zoledronic acid have not been substantiated by a recent Food and Drug Administration audit.^[10-13] Two other side-effects, namely osteonecrosis of the jaw (ONJ) and atypical fragility fractures (AFFs), however, warrant discussion.

The first report of an association between ONJ and the use of BPs was published in 2004, and it has subsequently become clear that up to 80% of cases occurred in patients with an underlying malignancy (often myeloma or breast cancer), and 90% were receiving high-dose intravenous BPs.^[14-16] In this regard, it is important to reiterate that such patients generally receive a dose of BPs that is *ten-fold* higher than doses used to treat osteoporosis. Other predisposing factors include dento-alveolar surgery and local oral disease (inflammation, cancer), systemic factors (advanced age, diabetes, renal impairment, smoking, alcohol), and a genetic predisposition. In patients with osteoporosis treated with BPs, the incidence of ONJ is extremely low (0.01 - 0.0004%) and probably not different from that of the general population. For this reason, NOFSA recommends^[11] that:

- Patients and dentists need to be reassured that ONJ is extremely rare in association with the doses of BPs approved for the treatment of osteoporosis. Whether BPs are administered orally or intravenously does not seem to affect the risk of ONJ.
- Good oral hygiene and regular dental visits are advisable. It is, however, not necessary to recommend a dental examination before starting BP therapy for osteoporosis. If major dental surgery is anticipated, it seems prudent to suggest that this be completed before starting BP treatment.
- In subjects already receiving a BP, dental implant surgery is not contraindicated. Some suggest stopping the BP, but there are no data to support this. The use of bone turnover markers has been suggested, but cannot be supported.
- In subjects with established ONJ, surgical treatment should be conservative, infection should be treated with appropriate antibiotics, and pain relief is important, as is referral to an experienced maxillofacial surgeon. Given the availability of alternative bone-active agents, it is probably reasonable to discontinue the BP.

Following earlier suggestions by Ott^[17] of atypical fractures after long-term alendronate therapy, in 2005 Odvina *et al.*^[18] (senior author Charles Pak) described nine cases of severely suppressed bone turnover with spontaneous non-spine fractures and delayed fracture healing. Subsequently numerous case reports, retrospective reviews and register-based national cohort studies have confirmed an increased prevalence of AFFs in patients receiving alendronate, prompting regulatory bodies in Europe, the UK and the USA to alert healthcare professionals to this association and to insist that product information for alendronate be updated to include a warning about AFFs. This syndrome is characterised by:^[17-20]

- A history of chronic alendronate use – limited data are available for the other BPs in support of a causal association with AFFs, but this probably reflects their lower use and the limited availability of long-term data.

- AFFs most often involve areas rich in cortical bone (e.g. subtrochanteric or diaphyseal femur, pelvic bones), and are sustained either spontaneously or following minimal trauma.
- A prodrome of pain and tenderness over the impending fracture site.
- Concomitant use of glucocorticoids or oestrogen.
- Quantitative bone histology shows severely suppressed bone turnover, similar to the so-called adynamic bone disease found in a subset of patients with chronic renal failure; serum biomarkers of bone turnover are usually decreased, but often not as markedly as the bone histology.
- Radiographs may show typical cortical stress fractures or a simple transverse or oblique fracture of the femur with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft.
- Bilateral disease is not infrequent – contralateral pathology may be evident on clinical assessment (e.g. tenderness over the femur shaft), standard radiographs or an isotope bone scan.
- History of delayed or absent fracture healing.

Correct management of this syndrome is difficult, given the current state of our knowledge. Clearly BP treatment needs to be discontinued in the event of an atypical fracture, and an alternative anti-fracture agent should be considered. Contralateral disease should be sought and may require intervention (e.g. prophylactic orthopaedic pinning). Appropriate measures to prevent the development of AFFs include greater awareness of the condition and possibly limiting the duration of BP treatment to 4 - 5 years. In this regard it is, however, imperative to note that BP-induced AFF is a rare phenomenon, with an estimated prevalence of around 1 in 1 000. Moreover, limiting BP treatment to <3 years has been shown to provide ineffective protection against conventional osteoporotic fractures. Much more harm may therefore emanate from the indiscriminate, premature discontinuation of BP treatment in an attempt to prevent AFF. There are no clear recommendations to circumvent this conundrum at present, other than to suggest that any osteoporosis treatment strategy should be reassessed following 4 - 5 years of BP therapy and the need for continued treatment with a BP or alternative anti-fracture agent appraised.

Stimulators of bone formation

Teriparatide

Parathyroid hormone (PTH 1-84) or the PTH fragment (hPTH 1-34), teriparatide, have been shown to be potent anabolic agents that stimulate osteoblastic bone formation (peaks within 3 - 6 months and is maintained for 18 - 24 months) and reduce vertebral and non-vertebral fracture risk. Osteoclastic bone resorption is also stimulated, but since this only peaks some 12 - 24 months later, an 'anabolic window' is created that results in a very significant increase in areal and volumetric bone mass, size and strength.^[21-27]

Teriparatide is used in the management of osteoporosis, but only for specific indications – these include failed anti-resorptive therapy, severe fracturing disease, and glucocorticoid-induced osteoporosis with a markedly decreased BMD. These specific indications have been published in position papers by NOFSA.^[24,25] The use of teriparatide is limited by its expense and certain contraindications. Long-term studies with high-dose PTH, administered lifelong to Fischer 344 rats, have demonstrated a dose-related increase in the risk of osteogenic sarcoma. All primate studies have failed to show a similar association, and osteosarcomas do not occur with increased frequency in humans with primary hyperparathyroidism, nor have they been noted in any of the trials performed in many thousands of patients treated with PTH for >3 years. To date, a single case of osteosarcoma has been reported in >300 000 patients

treated worldwide with PTH. It is therefore very unlikely that teriparatide is associated with any increased risk of osteogenic sarcoma. Nonetheless, regulatory bodies worldwide have limited the use of teriparatide to treat osteoporosis to an 18 - 24-month period (18 months in South Africa), following which alternative agents (e.g. a bisphosphonate) should be employed to preserve bone mass, which otherwise decreases rapidly after teriparatide has been discontinued. It has also been recommended that teriparatide should not be used in subjects with an increased risk of developing osteosarcoma (e.g. prior skeletal radiation), in patients with malignancy, in growing children, in pregnancy and lactation, in subjects with hypercalcaemia, and in individuals with impaired renal function (glomerular filtration rate <30 ml/min).

Nausea, headaches and leg cramps are not infrequent in patients treated with teriparatide. Hypercalcaemia occurs in up to 10% of patients, but hypercalciuria, hyperuricaemia and renal stone disease are rare.^[21-27]

Drugs with dual or complex actions on bone

Strontium ranelate

Strontium ranelate has a dual mode of action resulting in the stimulation of bone formation and inhibition of resorption. Large clinical studies such as the pivotal Spinal Osteoporosis Therapeutic Intervention (SOTI)^[28] and Treatment of Peripheral Osteoporosis (TROPOS)^[29] trials have demonstrated that this agent significantly increases BMD and decreases fracture risk at both the spine and hip over prolonged periods of time. Furthermore, the drug is effective in patients with only a modest decrease in BMD and also in the very old (>80 years).^[28-30]

Gastrointestinal side-effects, notably nausea and diarrhoea, occur frequently in the first 3 months of treatment but can usually be managed by slow titration of the dose. In pooled data from the SOTI and TROPOS studies, a small but significant (0.9% v. 0.6%) increased risk of venous thrombo-embolism (VTE) was documented, and although the cause of this is unknown, it is recommended that strontium ranelate is best avoided in patients at risk of VTE.

During post-marketing surveillance of patients treated with strontium ranelate, cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome as well as toxic epidermal necrolysis and Stevens-Johnson syndrome were reported^[31] – to date, <2 dozen cases from a total of more than a half million patient years of exposure have been documented. The DRESS drug hypersensitivity syndrome is not unique to strontium ranelate and is associated with a large number of commonly used drugs including the anti-epileptics and allopurinol. Since systemic involvement (hepatitis, nephritis, endocarditis) following continued use can be fatal, it is important to be aware of the association and to discontinue the drug if any significant skin disorder occurs within 2 - 3 months after initiating treatment.

In April 2013, the European Medicines Agency (EMA) released their report of a routine assessment conducted by their Pharmacovigilance Risk Assessment Committee (PRAC) on pooled data from seven studies in >7 500 women treated with strontium ranelate. Compared with placebo, those treated with strontium ranelate showed an increased risk of non-fatal myocardial infarction (1.7 v. 1.1%, with a relative risk of 1.6; 95% confidence interval 1.07 - 2.38).^[32] This increased risk was confined to patients with poorly controlled hypertension (blood pressure >160/90 mmHg) or known ischaemic heart disease (IHD). Based on the report of the PRAC, the EMA Committee for Medical Products of Human Use made certain recommendations regarding the indications for

and contraindications to strontium ranelate in the treatment of osteoporosis.^[32] Further evaluations are being conducted. Locally, these findings have been submitted to the Medicines Control Council (MCC), which is currently reviewing the data.

NOFSA's views on the matter can be summarised as follows:

- Strontium ranelate is a useful anti-fracture agent to manage patients with osteoporosis or those at high fracture risk, if the following precautions are adhered to:
 - Strontium ranelate should not be used in patients with a current or past history of IHD, peripheral arterial disease (PAD) and/or CVD, or in patients with uncontrolled (>160/90 mmHg) or untreated hypertension.
 - Before embarking on treatment with strontium ranelate, the presence of risk factors for CVD (e.g. dyslipidaemia, dysglycaemia/diabetes, obesity, hypertension, smoking) should be carefully assessed. If present, treatment with strontium ranelate should be undertaken only after careful consideration.
 - Risk factors for and/or the presence of CVD should be assessed at regular intervals during treatment, and treatment should be discontinued if the patient develops uncontrolled hypertension, IHD, CVD or PAD.

These recommendations of NOFSA will of course all be subject to the final recommendations from the MCC.

Conclusions

If it is used appropriately, the benefits of treatment of osteoporosis far outweigh the risks. Every patient with osteoporosis therefore deserves a thorough assessment and in-depth consideration of therapeutic options before initiating the most appropriate, most effective and safest treatment.

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Accepted 17 October 2013.