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Pharmacological Management of Osteoporosis in 2000

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ABSTRACT

Elderly patients with either low bone density or a prior low trauma fracture should be considered for therapeutic intervention to prevent further fragility fractures. Oestrogen replacement therapy remains the first choice for prevention of bone loss in early postmenopausal women with low bone density. However, in older postmenopausal women with existing fractures, oestrogen may not be acceptable or tolerated. In this group, low-dose oestrogen combined with calcium supplementation increases bone density and may be better tolerated. Other treatment options to prevent fragility fractures are firstly, the potent aminobisphosphonate, alendronate; secondly, the selective oestrogen receptor modulating drug, raloxifene; and thirdly, the less potent bisphosphonate, etidronate, or the active form of vitamin D, calcitriol.

For elderly men with osteoporosis, treatment with testosterone replacement therapy should be considered if hypogonadism is present. Although no data concerning antifracture efficacy exist, a bisphosphonate should be considered together with calcium in eugonadal osteoporotic men.

Supplementation with calcium and vitamin D (cholecalciferol or ergocalciferol) should be strongly considered in the housebound or institutionalised elderly of both sexes who have a high risk of vitamin D deficiency, osteomalacia and falling. Studies of vitamin D and calcium supplementation in such patients have shown that their risk of hip fracture is reduced. **Aust J Hosp Pharm 2000; 30: 111-15.**

INTRODUCTION

Osteoporosis is a largely silent epidemic afflicting both the Western World and the developing countries. It is defined as a skeletal disorder characterised by a reduction in bone mass and microarchitectural deterioration in bone tissue with a subsequent increase in bone fragility. In Australia 50% of women and 30% of men over the age of 60 years will sustain a fragility fracture due to osteoporosis throughout their remaining lifetime.¹ Over the last four years, the results of large trials with newer anti-osteoporotic drugs such as the bisphosphonates, alendronate and risedronate, and the selective oestrogen receptor modulating drug, raloxifene, have become available. In the public domain, the benefits of an increased dietary calcium intake have also been promulgated. As a

result, the risk/benefit ratio for these different treatment options and the number of patients needed to treat to prevent fractures are becoming clearer. In addition, anti-fracture efficacy data and data regarding both breast cancer risk and cardiovascular disease risk reduction from large placebo-controlled trials of oestrogen therapy will become available in seven years from the US Women's Health Initiative Study, at a cost of US\$1 billion. This will further assist clinical decision making in this area that is a burgeoning problem for many elderly Australians.

PREVENTION AND TREATMENT OF OSTEOPOROSIS

Recommendations for the prevention and treatment of osteoporosis in the elderly are similar to those earlier in life. It should be remembered that it is never too late to prevent a fracture and that all antiosteoporotic drugs are equally effective in elderly women as in younger women. In addition, most clinical studies of the treatment of postmenopausal osteoporosis have included elderly women who might normally be excluded from randomised, placebo-controlled clinical trials.

An adequate dietary calcium intake and vitamin D supplementation, if required, together with regular exercise to maintain muscle mass and balance are mandatory. Risk factors, such as smoking and an excessive alcohol intake, should be avoided. However, for the elderly with low bone density, especially if a low trauma fracture already exists, such measures may not prevent further fragility fractures and additional pharmacological therapy must be strongly considered.

Calcium

Several controlled trials have shown that calcium supplementation can prevent bone loss in postmenopausal women and this has been associated with a mild reduction in vertebral fracture risk in longer-term studies.² There is also recent evidence suggesting calcium supplementation potentiates the effect of oestrogen on bone density, enabling the oestrogen dose to be reduced.^{3,4} This may increase the acceptance of hormone replacement therapy (HRT) with oestrogen by elderly women.

Calcium absorption seems to be equivalent from all dietary sources, including milk, soy products and dietary calcium supplements. Calcium is better absorbed if taken with a slightly acidic drink such as orange juice. Calcium supplements also have a better antiresorptive effect when taken at night, but they should be separated as long as possible from bisphosphonates as calcium can hinder their absorption from the gastrointestinal

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tract. Most controlled trials of the newer antiosteoporotic drugs have used calcium as baseline therapy. It is therefore appropriate to add a calcium supplement or an increased dietary calcium intake to most of these drugs.

Vitamin D

A French study of the institutionalised elderly showed treatment with calcium and vitamin D supplements significantly reduced the rate of hip fractures;⁵ however, a similar effect was not shown in another European study of the community-dwelling elderly.⁶ Our own data from Melbourne indicate a substantial proportion of institutionalised, elderly people may be vitamin D deficient.⁷ The observed reduction in fractures in the French study may have reflected treatment of subclinical osteomalacia and secondary hyperparathyroidism rather than osteoporosis. Although not studied, the risk of falling may have been reduced secondary to an improvement in muscle tone and balance. Hence, vitamin D supplementation with either cholecalciferol or ergocalciferol should be strongly, if not routinely, recommended to prevent hip fractures in institutionalised or housebound elderly people who have limited exposure to sunlight.

Calcitriol

Calcitriol is the active form of vitamin D. Controlled trials of its effect on bone density have been inconsistent,^{8,9} although suboptimal doses may account for some of these discrepancies. In addition, a recent larger study suggests the effect on bone density is less than that seen with oestrogen.¹⁰ The use of calcitriol to treat osteoporosis is largely based on a single, large controlled trial of the efficacy of calcitriol in preventing vertebral fractures.¹¹ In that study, spinal fracture rates remained stable in calcitriol-treated patients, but increased in the calcium-treated patients. Calcitriol treatment may be most appropriate for patients with known or presumed calcium malabsorption. Greater increases in bone density are seen when calcitriol is combined with HRT than are seen with HRT alone.¹⁰ Although calcitriol is approved for osteoporosis in men in Australia, our recent small double blind, double placebo study suggested that calcitriol may be no better than calcium supplementation alone.¹² When using calcitriol, regular monitoring of plasma calcium concentrations is required because of the increased risk of hypercalcaemia, particularly in the elderly and in patients with renal impairment.

Oestrogen

Oestrogen, combined with a progestogen in women with an intact uterus, is still generally considered to be the first-line therapy for the prevention and treatment of postmenopausal osteoporosis. Continuous combined HRT is now the most commonly recommended form of HRT in Australia. Although calcium supplementation generally reduces bone loss, it is less effective in the early postmenopausal years. A number of controlled clinical trials with oestrogen have shown long-term increases in bone density of 5%, on average, over three years.¹³ Lower oestrogen doses may be effective with concomitant calcium as noted above.^{3,4} Only two randomised clinical trials have assessed the efficacy of oestrogen on reducing fractures.^{14,15} These indicated a 50% reduction in the rate of new vertebral fractures, although the number of patients with new vertebral fractures was similar. Sev-

eral epidemiological studies indicate the antifracture efficacy at all sites for oestrogen may be comparable to that of other agents.¹⁴ Thus, although it is likely oestrogen reduces fracture rates as well as increasing bone density, the results of large prospective controlled studies of the antifracture efficacy of oestrogen such as the National Institutes of Health-sponsored Women's Health Initiative will be required to confirm this expectation. These data will be available in seven years.

The absolute risk of breast cancer is slightly increased with oestrogen and the increase in risk depends on the duration of oestrogen use and age of the patient.

Raloxifene

Raloxifene is a selective oestrogen-receptor modulating drug and has stimulatory effects on oestrogen receptors in some tissues and inhibitory effects in other tissues. In addition to its action as an antiresorptive agent, it improves lipid profiles and reduces the incidence of primary, oestrogen receptor-positive breast cancer at 3.5 years.^{16,17} Importantly, raloxifene does not adversely affect the breast or uterus and a progestogen does not have to be co-administered. There is a tendency for hot flushes to increase and its other common side effects are leg cramps and a slightly increased risk of deep venous thrombosis, of a similar magnitude to that for oestrogen therapy (about 3/10 000).

Controlled clinical trials have shown only modest increases in bone density of 2-3%, somewhat less than those seen with HRT.^{17,18} Despite this, a 50% reduction in vertebral, but not peripheral fractures (excepting those at the ankle) has been observed.¹⁸ A reduction in bone resorption may be an independent effect of raloxifene contributing to the reduction in vertebral fracture risk. Longer-term studies are required to determine whether raloxifene decreases peripheral fractures or reduces the incidence of primary breast cancer in women at increased risk of the latter disease.

Anabolic Steroids

There have been no studies showing antifracture efficacy of nandrolone decanoate. Forearm bone mass increases modestly after nandrolone decanoate treatment and an open study showed nandrolone increased spinal and proximal femur bone mineral content, but these changes were antagonised by co-administration of intranasal salmon calcitonin.¹⁹ Nandrolone decanoate is still commonly used by general practitioners in Australia to treat osteoporosis in the elderly and it may help to reduce the risk of falls by increasing muscle mass although this remains to be proven.

Bisphosphonates

Bisphosphonates are orally active analogues of pyrophosphate that are currently used as second-line agents in postmenopausal women with osteoporosis who are unable to take HRT, or in whom HRT is ineffective. Bone resorption, as well as calcification of hydroxyapatite crystals in bone, are inhibited by bisphosphonates. Bisphosphonates act by inducing osteoclast programmed cell death or apoptosis. The more potent N-containing bisphosphonates interfere with the mevalonate pathway responsible for cholesterol synthesis.²⁰ Interestingly, HMG-CoA reductase inhibitors are more potent *in vitro* inhibitors of bone resorption than bisphosphonates.

Recent *in vivo* studies in rodents using subcutaneous or orally administered simvastatin and lovastatin have also demonstrated increased bone formation.²¹

All bisphosphonates are polar and as a result they have very low solubility. They should be taken with plain tap water alone at least half an hour before any food or fluid. Antacids and calcium supplements particularly interfere with their absorption.

Etidronate

Two studies used cyclical etidronate (400 mg/day for two weeks, then repeated every three months) in osteoporotic postmenopausal women.^{22,23} They showed increases in spinal bone mineral density (BMD) of 4-5% and a 50% reduction of vertebral fractures. Neither study examined hip fractures, nor non-vertebral fractures. However, a subsequent large retrospective cohort study of etidronate users and non-users found that hip and non-vertebral fractures were significantly reduced in the etidronate users.²⁴ Because etidronate also causes reduced mineralisation if given continuously, its administration must be cyclical to avoid osteomalacia.

Alendronate

Larger studies using the more potent aminobisphosphonate, alendronate, have consistently demonstrated anti-fracture efficacy in women with postmenopausal osteoporosis and at least one vertebral fracture.^{25,26} Spinal and femoral neck BMD increased by about 8% and 5% at three years, respectively. Significant increases in spinal BMD occur as early as the duration of one remodeling cycle (about 3 months) in women with low BMD. In addition to a reduction in vertebral fractures by 47%, hip fractures and non-vertebral fractures were also reduced by 28% and 51%, respectively. Forearm fractures were reduced by 48%. The number of women with one baseline vertebral fracture needing treatment for five years to prevent one fracture are 16, 26 and 91 for vertebral, any clinical and hip fractures, respectively (Table 1).²⁷

Table 1. Number of women with a baseline spinal fracture needed to treat (NNT) with alendronate for 5 years to prevent one fracture²⁷

Category	NNT to prevent one vertebral fracture	NNT to prevent one clinical fracture
Baseline femoral neck bone mineral density		
<0.59 g/cm ²	7	10
>0.59 g/cm ²	13	30
Number of baseline vertebral fractures		
1	16	26
2 or more	4	6
Age		
<75 years	9	13
>75 years	8	15

For postmenopausal women who do not have a vertebral fracture, the absolute reduction in fracture risk depends on the skeletal site. Alendronate was most efficacious in women who had a baseline t-score at the femoral neck of less than -2.5.²⁸ The t-score is defined as the

number of standard deviations (SD) above or below the mean BMD value for young healthy adult white women. The number needed to treat (NNT) to prevent a fracture in women with osteoporosis of the femoral neck is similar to that in women with one pre-existing vertebral fracture. There was a 36% reduction in clinical fractures in women with baseline osteoporosis at the femoral neck (>2.5 SDs below the normal young adult mean) (NNT for 4.25 years to prevent one clinical fracture = 15) and a 56% reduction in hip fracture (NNT = 81). Interestingly, there was also a trend for an increased number of wrist fractures in women with a t-score of more than -2.0 treated with alendronate. BMD decreases, but not to baseline, in the first 2 years of cessation of alendronate. In addition, women who have increases in BMD of greater than 3% at 1 or 2 years have the greatest reduction in fracture events.²⁹

There was no increase in upper gastrointestinal adverse events in randomised clinical studies of alendronate; however, like pamidronate (another aminobisphosphonate), alendronate may cause upper gastrointestinal irritation.³⁰ Oesophagitis and oesophageal ulceration are particularly concerning and can be largely avoided by taking alendronate with a glass of water at least half an hour before a meal and remaining upright for one hour. Alendronate may also cause oral ulcerations if it is inadvertently sucked or chewed.

A recent advance in alendronate therapy is the substitution of a weekly 70 mg tablet instead of a daily dose of 10 mg. Effects on BMD of this preparation are similar to those of the 10 mg tablet regimen.³¹

Oestrogen and Alendronate

Some women receiving HRT may continue to be at risk of fracture due to low BMD, falling or other factors. In this group there are now data to show that the addition of alendronate to oestrogen can result in further increases in BMD. After 12 months, alendronate increased spinal and femoral trochanter BMDs by up to an additional 2.6% and 2.2%, respectively. However, the additional increase in femoral neck (FN)-BMD of approximately 1% was not significant.³²

Risedronate

Risedronate is available for osteoporosis treatment in Europe and is likely to be released in Australia within one year. In postmenopausal women with at least one vertebral fracture the addition of risedronate 5 mg/day to calcium 1000 mg/day decreased vertebral fractures by 41% at three years.³³ The absolute reduction in fracture risk was 5%. Non-vertebral fractures were decreased by 39%. Increases in BMD were greater than placebo by 4.3%, 2.8% and 1.6% at the lumbar spine, femoral neck and mid-shaft of the radius, respectively. The incidence of moderate to severe upper gastrointestinal events was similar in both groups, as it was in the clinical studies involving alendronate. Post-marketing studies are required to determine whether the incidence of upper gastrointestinal events are less with risedronate than with alendronate.

Pamidronate

Pamidronate is the only intravenous bisphosphonate currently available and may be used in patients intolerant of oral bisphosphonates. Pamidronate at a dose of

30 mg intravenously every three months resulted in increases in spinal and hip BMDs of 6.4% and 4.1%, respectively over 7.8 months.³⁴ No fracture data are available and the optimal duration of treatment is unknown.

Newer Indications for Bisphosphonates in Osteoporosis

Osteoporosis in Men

A recent randomised, controlled trial of alendronate in eugonadal or hypogonadal elderly osteoporotic men demonstrated increases in spinal, femoral neck and femoral trochanter BMDs of 7.1%, 2.5% and 4.4%, respectively. Height loss was prevented by alendronate and there was a non-significant trend for a reduction in radiographic vertebral fracture rates.³⁵ Retrospective cohort studies have suggested that etidronate may also be an effective treatment for osteoporosis in men.³⁶

Glucocorticoid-Induced Osteoporosis

A mechanism of bisphosphonate action in glucocorticoid-induced osteoporosis may be the prevention of glucocorticoid-induced osteoblast and osteocyte apoptosis. Two large multicentre trials of etidronate (in men and women aged 19-87 years) and alendronate (in men and women aged 17-83 years) in glucocorticoid-induced osteoporosis show that both drugs increase spinal BMD at 12 months.^{37,38} Only alendronate increased femoral neck BMD, but both significantly increased femoral trochanter BMDs. There was a trend for a reduction in vertebral fractures in postmenopausal women in both studies, but this was not significant. Risedronate has recently been reported to decrease vertebral fractures in subjects with glucocorticoid-induced osteoporosis, as well as increasing BMD.³⁹

Prevention of Postmenopausal Bone Loss

Alendronate prevents bone loss in early postmenopausal women at all sites except the forearm.⁴⁰ However, BMD decreased more at the forearm in women given placebo and alendronate is effective at reducing the rate of forearm fractures in postmenopausal women with osteoporosis. Risedronate also increases spine and hip BMDs and decreases bone turnover in early postmenopausal women.⁴¹ However these bisphosphonates should be seen as third-line drugs for the prevention of menopausal bone loss behind HRT and raloxifene.

Other Drugs

Fluoride is used for the treatment of osteoporosis in Europe. Uncertainties about the correct safe dose to use means that it is not available in Australia. Intranasal calcitonin causes small increases in bone density, but reduced the risk of vertebral fracture in one study.⁴² Tibolone has tissue dependent, oestrogenic or androgenic effects and may be a useful alternative to HRT or raloxifene for the prevention of menopausal bone loss.⁴³ Like intranasal calcitonin it is not yet available for use in Australia.

EVALUATION AND MONITORING

Treatment responses are currently best monitored by repeating bone densitometry measurements. The interval between measurements should probably be two years, as recent studies show 'regression to the mean'

at one year; however, in practice bone density is re-measured one year after commencing or changing therapy. It is likely that, in the near future, the measurement of either a serum or urine biochemical marker of bone turnover at six months after initiation of treatment will be useful in monitoring response to therapy as well as compliance with medications. Currently using bone density as a measure, it is probably prudent to wait at least 24 months before concluding a treatment is ineffective. Treatment should be continued for at least four years for bisphosphonates and raloxifene and probably longer for oestrogen.

SUMMARY

In postmenopausal women, oestrogen remains the first-line therapy. In older postmenopausal women, especially those with pre-existing fragility fractures, the risk of further fragility fractures is highest and other treatments, based on the current evidence, include alendronate, raloxifene, the less potent bisphosphonate, etidronate, or the active form of vitamin D, calcitriol. Vitamin D and calcium supplements are strongly recommended for housebound or institutionalised elderly people, who are at highest risk of vitamin D deficiency. Dietary calcium supplementation should also be used in conjunction with oestrogen, raloxifene and the bisphosphonates. For postmenopausal women with severe osteoporosis, combination therapy with an oestrogen and a bisphosphonate should be considered.

For hypogonadal men with osteoporosis, testosterone replacement therapy should be considered. Although no antifracture efficacy data exist, in eugonadal osteoporotic men bisphosphonates and calcium supplementation should be considered instead.

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