Bisphosphonates – clinical applications in osteoporosis

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SYNOPSIS

Bisphosphonates are effective treatments for the prevention and treatment of osteoporosis. In particular, alendronate and risedronate increase bone mineral density and reduce the spinal fracture rate to approximately 50% of that in controls, within one year. A less potent, ‘first generation’ bisphosphonate, etidronate, has also shown anti-fracture efficacy. Alendronate also reduces fracture rates at the hip and other non-vertebral sites in osteoporotic postmenopausal women. Pamidronate is available for intravenous therapy and ibandronate and zoledronate may also become available for injection. Current research studies are examining new compounds, treatment regimens and the combination of bisphosphonates with other drugs such as oestrogen, which currently remains the first-line therapy for the prevention and treatment of osteoporosis in women.

Index words: bone mineral density, fractures, etidronate, alendronate, risedronate.

Introduction

Bisphosphonates inhibit bone resorption. The structure of the \( R_2 \) side chain determines the potency of bisphosphonates (see ‘Bisphosphonates – mechanisms of action’ Aust Prescr 2000;23:130–2). Differences in the potency of the different bisphosphonates can be accommodated by the use of appropriate doses. Their effect on osteoclasts makes the bisphosphonates useful in several conditions including osteoporosis where bone metabolism is abnormal.

In selecting women for treatment, the presence of a fragility fracture and/or low bone mineral density (BMD) are the best independent predictors of future fracture risk. In elderly women, the presence of a fragility fracture is the best predictor of future fracture risk. In perimenopausal women the harm:benefit ratio is less clear. Hormone replacement therapy may be the preferred treatment for perimenopausal women with a fragility fracture or low BMD. It remains the first-line therapy for the prevention and treatment of osteoporosis.

Hip fracture is the major clinical problem in osteoporosis and low BMD at the femoral neck is a good predictor of future hip fracture.1 Only vitamin D and calcium supplementation in the institutionalised elderly, or alendronate therapy in postmenopausal women with osteoporosis have been demonstrated to reduce hip fractures.

Evidence of efficacy in postmenopausal osteoporosis

Etidronate

The first randomised controlled trials of bisphosphonates in postmenopausal osteoporosis used cyclical etidronate (400 mg/day for two weeks, then repeated every three months). This treatment resulted in increases in spinal BMD of 4–5% and a 50% reduction of vertebral fractures in the first and second year of these three-year studies. However, after three years, no reduction in vertebral fractures was seen.2 These trials did not study hip or non-vertebral fractures, however, a subsequent large retrospective cohort study found that these fractures were significantly reduced by etidronate.3

Alendronate

Alendronate is a more potent bisphosphonate than etidronate. A number of large studies have found that alendronate can prevent further fractures in women with postmenopausal osteoporosis and at least one vertebral fracture.4,5

Significant increases in spinal BMD occur as early as the duration of one remodelling cycle (about three months) in women with low BMD. Biochemical markers of bone resorption are reduced to levels seen in premenopausal women after only four weeks of treatment. Spinal and femoral neck BMD increase by about 8% and 5% after three years of therapy.

The absolute and relative reductions in fracture risk (see box) vary with the fracture site in women with postmenopausal osteoporosis.

<table>
<thead>
<tr>
<th>Definitions of relative risk reduction and number needed to treat to prevent one incident</th>
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<tbody>
<tr>
<td>Relative risk reduction = ( \frac{\text{placebo incidence} - \text{treatment incidence}}{\text{placebo incidence}} )</td>
</tr>
<tr>
<td>Number needed to treat = ( \frac{100}{\text{placebo incidence} - \text{treatment incidence}} )</td>
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osteooporosis and at least one vertebral fracture. In addition to reducing the relative risk of vertebral fractures by 47%, alendronate reduces hip fractures by 28% and non-vertebral fractures by 51%. Forearm fractures are also reduced by 48%. For women with a history of vertebral fracture, 16 need to be treated for five years to prevent one further vertebral fracture. To prevent one hip fracture the number needed to treat (NNT) is 91 (Table 1).

The lower (or more negative) the T-score, the greater is the deficit in bone density. For postmenopausal women who do not have a vertebral fracture, the T-score at which treatment can be recommended is not clear. Alendronate was most efficacious in women who had a baseline T-score at the femoral neck which was more negative than –2.5. In these women there was a 36% reduction in clinical fractures (NNT = 15) and a 56% reduction in hip fracture (NNT = 81) (Table 2). This compares with an NNT of 10 for women with one pre-existing vertebral fracture and low femoral neck BMD. The duration of treatment probably needs to be greater than four years in postmenopausal women with low bone density alone. Women who have increases in BMD of greater than 3% after one or two years have the greatest reduction in fractures. Alendronate showed no efficacy in women with a BMD T-score that was more positive than –2.5. In this group, there was an increase in forearm fractures.

Quantitative bone histomorphometry does not show that women treated with alendronate have abnormal mineralisation. Their BMD decreases, but not to pretreatment levels, in the first two years after stopping alendronate.

Oestrogen and alendronate

Some women taking hormone replacement therapy may continue to be at risk of fractures because of a low BMD or other factors. There are now data from at least two studies showing that the addition of alendronate to oestrogen can result in further increases in the BMD of these women. After 12 months, alendronate increased the BMD by up to an additional 2.6% in the spine and 2.2% in the femoral trochanter. However, the additional increase of approximately 1% in the BMD of the femoral neck was not significant and there are no data to show that adding alendronate to oestrogen further reduces fracture rates.

Risedronate

In postmenopausal women with at least one vertebral fracture risedronate increases BMD. Increases were 4.3% greater than placebo in the lumbar spine, 2.8% in the femoral neck and 1.6% in the shaft of the radius. Vertebral fractures were decreased by 41% after three years. The absolute reduction in fracture risk was 5%. Non-vertebral fractures were decreased by 39% (3.2% absolute risk decrease). The NNT to prevent a fracture was similar to that of alendronate (Table 1).

Pamidronate

For patients who are intolerant of oral bisphosphonates, pamidronate is the only intravenous bisphosphonate currently available. A dose of 30 mg intravenously every three months increases spinal BMD by 6.4% and BMD in the hip by 4.1%, over approximately eight months. The optimal duration of treatment is unknown and no fracture data are available. BMD falls but does not return to baseline levels after stopping pamidronate.

Selection of patients for bisphosphonate therapy

When deciding to use a bisphosphonate, the age and menopausal status of the woman should be considered in

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**Table 1**

<table>
<thead>
<tr>
<th>Category</th>
<th>NNT to prevent one radiological vertebral fracture</th>
<th>NNT to prevent one clinical fracture</th>
<th>NNT to prevent one hip fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (5 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline bone density at femoral neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score ≤–3.0 approximately (&lt;0.59 g/cm²)</td>
<td>7</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>T-score ≥–3.0 approximately (&gt;0.59 g/cm²)</td>
<td>13</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Number of baseline vertebral fractures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>26</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yrs</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>&gt;75 yrs</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Risedronate (3 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of baseline vertebral fractures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1</td>
<td>20</td>
<td>31</td>
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</table>

NNT = Number needed to treat
addition to the severity of her osteoporosis. There are no data showing anti-fracture efficacy of bisphosphonates in premenopausal women with osteoporosis. Peri- or early postmenopausal women may prefer treatment with oestrogen to reduce symptoms of oestrogen deficiency. Postmenopausal women who are more than 75 years old are less likely to accept hormone replacement therapy. It should be noted that bisphosphonates are equally efficacious in younger and older postmenopausal women and that it is ‘never too late’ to prevent a fracture.

Dosing

Adequate calcium and vitamin D nutrition in the diet are prerequisites for treatment with bisphosphonates. All the studies of bisphosphonates have included at least 600 mg of calcium so all patients should take supplemental calcium with their bisphosphonate. Measures to minimise falls, including regular exercise to maintain balance, are also important to prevent fractures.

The bisphosphonates have very low solubility and low oral bioavailability (approximately 0.5%). Patients should only take them with plain tap water at least half an hour before any food or fluid. Absorption is particularly reduced by antacids and calcium supplements.

Appropriate dosing is critical to ensure anti-fracture efficacy. Too low a dose may reduce anti-fracture efficacy as seen in clinical trials of tiludronate. High doses, in animal studies, impaired repair of bone microfracture damage and caused increased bone fragility.

Adverse effects

Bisphosphonates can cause gastrointestinal upsets. The incidence of moderate to severe upper gastrointestinal events with risedronate is similar to placebo as it was in the clinical studies involving alendronate. However, 35% of subjects in the risedronate trial had ongoing, or a history of, gastrointestinal disorders on entry to the study. In the alendronate studies, subjects with specific gastrointestinal disorders were excluded from the study. This supports the gastrointestinal safety of risedronate, but it will require validation by post-marketing studies.

Although there was no increase in upper gastrointestinal adverse events in randomised clinical studies, alendronate may cause upper gastrointestinal irritation. Oesophagitis and oesophageal ulceration are particularly concerning. They probably result from gastro-oesophageal reflux and acidification of the oesophagus, causing the release of alendronic acid. To avoid this, patients should take alendronate with a glass of water at least half an hour before a meal and remain upright for one hour. Alendronate may also cause oral ulcerations if it is inadvertently sucked or chewed.

Bisphosphonates can also alter electrolyte balance. The drugs should therefore be used with caution if renal function is impaired.

Monitoring of treatment and treatment failure

Treatment with bisphosphonates is currently best monitored by bone densitometry. There is growing evidence that a measurement at two years after starting therapy is a better indicator of response than a measurement at one year. Currently tests for bone turnover lack sensitivity in the individual patient.

Patients may fail treatment with bisphosphonates and continue to sustain fragility fractures. The decision to stop the bisphosphonate will depend on the BMD and the timing of the fracture in relation to the start of therapy.

Most of the anti-fracture efficacy of bisphosphonates occurs within one to two years of starting therapy. To maintain this benefit, treatment may need to continue for at least five years. If the patient’s bone density does not respond during the first two years of therapy, or if she continues to sustain fractures, another treatment should be considered.

Treatment with a bisphosphonate need not stop following a fracture. There is no evidence in humans to suggest that fracture healing is impaired by bisphosphonates.

Other possible indications for bisphosphonates

Osteoporosis in men

Retrospective cohort studies have suggested that etidronate may be an effective treatment for osteoporosis in men. Alendronate has been studied in a recently published

| Table 2 |
|-------------------|-------------------|
| **Number of women with low bone density who need to be treated for four years to prevent one fracture** |
| **Category** | **NNT to prevent one clinical fracture** | **NNT to prevent one hip fracture** |
| Alendronate | | |
| Baseline bone density at femoral neck | | |
| T-score ≤–2.5 | 15 | 81 |
| T-score ≥–2.0 | 30 | No effect |
| NNT = Number needed to treat | | |
randomised, controlled trial of men with primary osteoporosis or osteoporosis related to hypogonadism. There were increases in the BMD of the spine (7.1%), femoral neck (2.5%) and femoral trochanter (4.4%). Height loss was prevented by alendronate and there was also a reduction in the incidence of radiographic vertebral fractures.9

Glucocorticoid-induced osteoporosis
Bisphosphonates may prevent glucocorticoid-induced osteoblast and osteocyte apoptosis. Two large multicentre trials of etidronate and alendronate in glucocorticoid-induced osteoporosis show that both are effective at increasing spinal BMD at 12 months.10,11 Only alendronate increased BMD in the femoral neck, but both drugs significantly increased the BMD in the femoral trochanter. There was a non-significant trend for a reduction in vertebral fractures in postmenopausal women in both studies.

Risedronate increases BMD.12 A daily dose of 5 mg has also recently been reported to significantly decrease vertebral fractures by 70% in patients with glucocorticoid-induced osteoporosis.13 In a preliminary uncontrolled study in glucocorticoid-induced osteoporosis, pamidronate significantly increased spinal BMD by 4.7% at one year. There was no change in hip BMD. By comparison, calcitriol therapy prevents spinal bone loss in glucocorticoid-induced osteoporosis. However, it does not prevent bone loss from the femoral neck, nor are there anti-fracture efficacy data.

Prevention of postmenopausal bone loss
Women with low BMD who are either intolerant of or unwilling to accept therapy with either oestrogen or raloxifene (see ‘New drugs’ Aust Prescr 1999;22:96–7) would be suitable for treatment with a bisphosphonate. Bisphosphonates have been shown to prevent postmenopausal bone loss. In early postmenopausal women without osteoporosis, alendronate prevents bone loss at all sites except the forearm. In similar women risedronate increases the BMD of the spine and hip, and decreases bone turnover.14 In studies of these drugs fracture reduction was not an end-point.

Future directions
Current clinical studies are examining the comparison of intravenous and oral dosing, and the optimal frequency and duration of oral dosing. In the future there may be additional indications for this class of drugs as they affect metabolic pathways throughout the body, not just in bone cells.

REFERENCES

Further reading

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Self-test questions
The following statements are either true or false (answers on page 139)

9. Bisphosphonates should be taken after food to reduce the risk of oesophagitis.
10. Alendronate may increase forearm fractures in some women with low bone density.