Fortnightly Review

The therapeutic use of bisphosphonates

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Bisphosphonates are synthetic analogues of pyrophosphate, a naturally occurring substance which inhibits the mineralisation of bone. The therapeutic potential of these compounds, however, lies in their ability to inhibit bone resorption, and over the past two decades several bisphosphonates have been developed and evaluated in hyperresorptive states, particularly Paget's disease, hypercalcaemia of malignancy, and osteoporosis.[1]

Summary points

- Bisphosphonates are non-biodegradable synthetic analogues of pyrophosphate which inhibit bone resorption. The potency of their antiresorptive effect varies widely with different compounds
- Intestinal absorption of bisphosphonates is low (< 1% to 10%) and their half life in the skeleton very long
- The main therapeutic application of bisphosphonates is in diseases characterised by increased bone turnover. They are the treatment of choice in Paget's disease and hypercalcaemia of malignancy
- Bisphosphonates also show promise in osteoporosis, particularly in its prevention. Beneficial effects on fracture rate, however, have not been firmly established
- The toxicity of bisphosphonates is low and varies between compounds. Adverse effects on bone mineralisation occur with some bisphosphonates at doses used to inhibit bone resorption
- The development and evaluation of new bisphosphonates is an important topic in osteoporosis research. Crucial and unresolved issues include the optimal regimens (continuous *v* intermittent), comparative efficacy of different compounds, and the potential to produce anabolic effects in bone

Structure of bisphosphonates

Bisphosphonates are characterised by two carbon-phosphorus bonds, the carbon atom replacing the oxygen in the P-O-P (phosphorus-oxygen-phosphorus) bond of pyrophosphate (fig 1) and the P-C-P (phosphorus-carbon-phosphorus) bond conferring resistance to chemical and enzymatic hydrolysis. Different substitutions on the carbon atom have created several different bisphosphonates, each with its own individual pharmacological properties. The first bisphosphonate to be used therapeutically was etidronate, and subsequently many others have been developed. In order of increasing potency of antiresorptive activity the main bisphosphonates are etidronate, tiludronate, clodronate, pamidronate, alendronate, and risendronate.

Effects of bisphosphonate on bone

BONE RESORPTION

The antiresorptive potency of the different compounds of bisphosphonate varies considerably. The antiresorptive effect is believed to be cell mediated but its mechanism has not been clearly established. Effects on osteoclast differentiation, recruitment, and activity have all been reported, and recent evidence suggests that effects on bone resorption are also mediated, at least in part, via osteoblastic cells.[2,3] The considerable variations in antiresorptive potency between bisphosphonates may be attributable to different biochemical effects at the cellular level. The inhibitory effect is seen both for endogenous bone resorption and for resorption stimulated by agents such as parathyroid hormone, calcitriol, cytokines, and prostaglandins.

INHIBITION OF BONE MINERALISATION

Bisphosphonates have a strong affinity for hydroxyapatite crystals and in fairly high doses inhibit calcification of bone in vivo by physicochemical mechanisms. The ability to inhibit mineralisation varies considerably between bisphosphonates and is not related to antiresorptive potency.

Pharmacokinetics

Bisphosphonates are not metabolised, and etidronate, clodronate, pamidronate, and alendronate seem to be absorbed, excreted, and stored unchanged.

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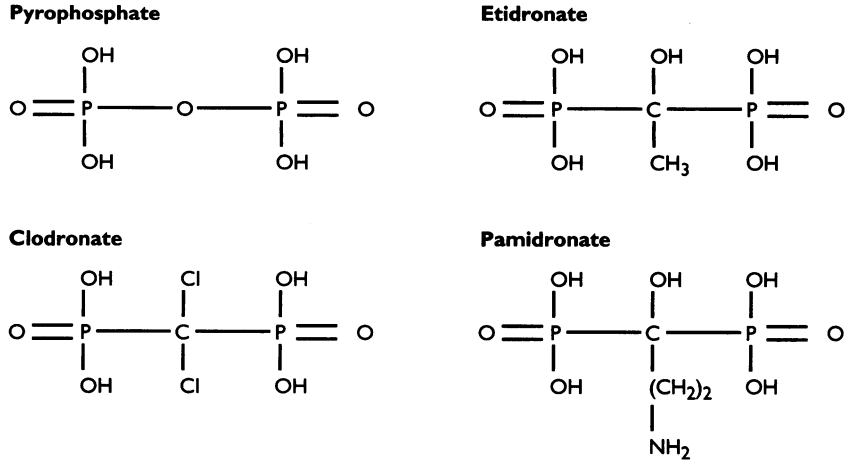

FIG 1—*Chemical structure of pyrophosphate and three bisphosphonates*

Structure, effects, and pharmacokinetics of bisphosphonate

- Bisphosphonates are synthetic analogues of pyrophosphate, characterised by a P-C-P (phosphorus-carbon-phosphorus) bond which renders them resistant to hydrolysis
- Intestinal absorption is poor (< 1% to 10%), plasma clearance rapid, and skeletal half life very long
- Bisphosphonates have inhibitory effects on bone resorption and bone mineralisation. The potency of these effects varies greatly with different compounds
- Bisphosphonates reduce bone turnover, leading to a transient increase in bone mass. It is uncertain whether they also have anabolic effects on bone

However, the side chains of some other compounds may be modified. Intestinal absorption is poor, varying from less than 1% to 10%, and is further reduced by concurrent ingestion of food, especially products containing calcium. Plasma clearance is rapid (half life around two hours) because of rapid uptake of 20-60% of the absorbed fraction into the skeleton. The remainder is excreted in the urine. The half life in bone is very long, release of bisphosphonates occurring only after resorption of bone into which the compounds have been taken up. Some bisphosphonates may thus remain in the skeleton for life.

Effects on bone remodelling

The changes in bone remodelling induced by bisphosphonates are particularly relevant to their long term use in the prevention and treatment of osteoporosis. Bone remodelling entails the removal by osteoclasts of a quantum of bone followed by the formation and mineralisation of osteoid, within the cavity so formed, by osteoblasts. This sequence occurs at discrete sites on the cancellous bone surface termed bone remodelling units. The temporal relation is that of resorption followed by formation (coupling), while balance describes the equality, in steady state conditions, of the amounts of bone resorbed and formed within individual remodelling units. The initial stage of remodelling requires the process of activation, in which the bone surface is prepared for resorption by retraction of the lining cells and enzymatic removal of the thin collagenous membrane covering the surface. A complete remodelling cycle in normal human adult bone takes around four to seven months.

The cellular mechanisms of bone loss differ in osteoporosis according to pathogenesis. Increased bone turnover resulting from an increase in activation frequency represents quantitatively the most important mechanism of bone loss in several forms of osteoporosis, including that associated with oestrogen deficiency. A negative remodelling imbalance also often occurs and is particularly characteristic of postmenopausal osteoporosis.[4] There is much evidence that bisphosphonates reduce bone turnover, leading to a transient increase in bone mass as a result of formation within existing resorption cavities (fig 2). However, their effects on remodelling balance are less well defined and cannot be deduced from biochemical markers, as is the case for bone turnover.

Histomorphometric assessment of the completed resorption depth and amount of bone formed within individual remodelling units is the only means by which remodelling balance can be established. These data are sparse and mostly insufficiently long term to reflect accurately steady state changes. After 60 weeks of treatment with intermittent cyclic etidronate and calcium Storm *et al* reported an improvement in remodelling balance due to a decrease in resorption depth. However, the wall width, which represents the amount of bone formed within individual remodelling units, was unchanged by treatment in this and two other studies.[5-7] Further long term data are required to establish whether bisphosphonates have anabolic effects on bone mass. The pattern of change in bone density in studies conducted for three or more years is consistent with a predominantly antiresorptive action and does not support appreciable anabolic effects.

Therapeutic applications of bisphosphonates

OSTEOPOROSIS

There is increasing interest in the use of bisphosphonates for the prevention and treatment of osteoporosis.[8,9] The effects of these compounds on bone remodelling suggest that the greatest benefits should be achieved when bone turnover is increased, though this has not been formally tested. In addition, bisphosphonates are most likely to be effective in prevention of bone loss rather than in the treatment of established disease, which requires restoration both of bone mass and of structure.

Postmenopausal osteoporosis

In many earlier studies of bisphosphonate treatment in osteoporosis the regimen used was based on the ADFR concept, originally introduced by Frost.[10] This entails the activation (A) of remodelling, followed by depression (D) of bone resorption, a period free (F) of treatment, and a repeat (R) of the cycle. In most studies phosphate was used as an activator and etidronate as an inhibitor of bone resorption. Overall, the effects on bone volume were neutral or negative.

Recently two randomised, placebo controlled trials of cyclic intermittent etidronate have been reported in women with postmenopausal osteoporosis.[11,12] In both, etidronate was given for two weeks in a cycle of about 13 weeks. Calcium supplementation was given in both studies, but in one phosphate was given as an activator for three days before etidronate. Spinal bone density increased in both studies by around 1·0-2·5% per annum, while bone density in the proximal femur (assessed in only one study) showed small but statistically significant increases in the treated group.[13] Adding phosphate to the regimen did not appear to affect changes in bone density.

Though significant reductions in vertebral fracture were claimed in both studies, neither had adequate

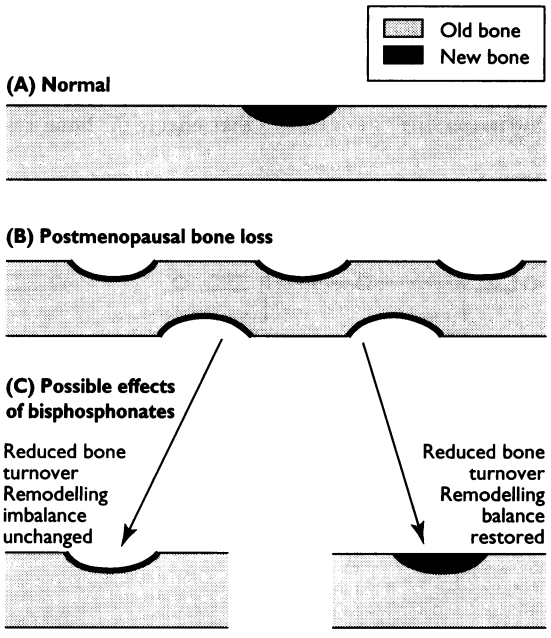

FIG 2—*Possible effects of bisphosphonates on bone remodelling*

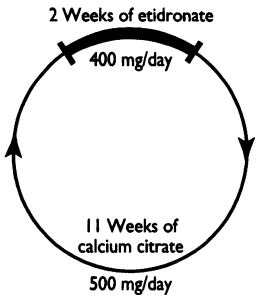

FIG 3—*Regimen of intermittent cyclic etidronate-calcium. Cycle is repeated four times yearly*

power to prove this. The question of whether cyclic intermittent etidronate protects against vertebral fracture must therefore remain open. It should also be noted that there is no evidence at present that this regimen protects against other osteoporotic fractures, particularly those of the hip and wrist. Cyclic intermittent etidronate-calcium is marketed in Britain as Didronel PMO and has a product licence for the treatment of postmenopausal spinal osteoporosis. The regimen used is shown in figure 3.

Other, more potent bisphosphonates are currently being evaluated in osteoporosis. At doses which have equipotent antiresorptive effects to etidronate they produce less inhibition of mineralisation. Though intermittent etidronate in the doses described does not seem to have adverse effects on mineralisation after three years, this remains a potential concern with longer term treatment. Pamidronate given intermittently or continuously increases bone mass in the spine and femoral trochanter, though no appreciable effect was seen in the femoral neck, Ward's triangle, or radial shaft after 18 months of treatment.[14,15] In placebo controlled randomised studies in women with postmenopausal osteoporosis significant increases of 3-6% in spinal and femoral bone density were reported after one year of continuous alendronate treatment,[16] and continuous tiludronate given for six months preserved spinal bone mass for one year (mean increase 1·33%).[17] As yet there are no data on the effects of these bisphosphonates on fracture risk at any site.

Corticosteroid induced osteoporosis

Both intermittent etidronate and either intermittent or continuous pamidronate have beneficial effects on bone mass in patients taking corticosteroids. The first prospective randomised controlled study was reported by Reid *et al* in 1988.[18] Significant increases in metacarpal and spinal bone mass were shown after one year's treatment with oral pamidronate and were maintained at two years.[19] Using intermittent intravenous pamidronate, Gallacher *et al* reported significant increases in bone density of the lumbar spine but not of the femur after one year in an uncontrolled study of 17 patients with corticosteroid dependent lung disease.[20]

Similar results have been obtained with intermittent etidronate, increases in vertebral bone density being reported in corticosteroid treated patients.[21] In those studies in which femoral bone density has been assessed, however, no benefit has been reported at this site. However, most of these studies have been uncontrolled, short term, and fairly small, and longer term studies are required to clarify the effects of bisphosphonates on femoral bone mass in these patients. The effects of bisphosphonates on fracture rate in corticosteroid treated osteoporosis have not been established.

Bisphosphonates in osteoporosis

- Cyclic intermittent etidronate produces beneficial effects on bone mass in the spine and femur in postmenopausal osteoporosis. A cyclic intermittent etidronate-calcium regimen is now licensed for use in postmenopausal osteoporosis in Britain
- Beneficial effects of this regimen on vertebral fracture rate are likely but remain unproved. There is no evidence for reduced fracture rate at the hip or wrist
- Newer bisphosphonates, including pamidronate, alendronate, and tiludronate, also produce small increases in spinal bone mass in postmenopausal osteoporosis
- In corticosteroid treated patients both etidronate and pamidronate prevent spinal bone loss, though positive effects on femoral bone mass have not been shown
- The optimal regimen for bisphosphonates in osteoporosis has not been determined. Long term effects on bone mineralisation and bone turnover require further evaluation

PAGET'S DISEASE

Paget's disease is characterised by an increase in bone resorption, manifested both by increased bone turnover and by an increase in the size of individual resorption cavities. The number and size of osteoclasts present are greatly increased. The aetiology of the disease is not established, though a viral origin has been proposed. Paget's disease is focal, usually affecting several skeletal sites.

Bisphosphonates have become the treatment of choice for Paget's disease, being superior to calcitonin in terms of response rate, degree and duration of remission, and lack of the secondary resistance which occurs in up to one fifth of patients taking calcitonin.[22,23] Response is dose related and the duration of remission may extend for up to two years. This prolonged remission is likely to result from the retention and subsequent low release of bisphosphonates from bone after its administration. The effectiveness of retreatment after relapse is similar to that of the initial course.

Bisphosphonates in Paget's disease

- Bisphosphonates are highly effective in Paget's disease. The response is dose related and remission after a course extends for up to two years
- Etidronate is the only bisphosphonate licensed for the treatment of Paget's disease in Britain. It suppresses serum alkaline phosphatase activity by around 40-60% in most cases but its use, particularly at doses >10 mg/kg/day, is associated with adverse effects on bone mineralisation and increased risk of fracture in some cases
- Evaluation of newer bisphosphonates for Paget's disease has indicated greater disease suppression, though adverse effects on bone mineralisation have been reported with pamidronate

Disease activity and its changes during treatment can be monitored biochemically by using serum alkaline phosphatase and urinary hydroxyproline or the collagen cross links deoxypyridinoline and pyridinoline as markers of bone turnover. The rate of decrease of serum alkaline phosphatase activity and the degree of suppression achieved by treatment are positively related and the initial disease activity inversely related to the duration of remission. Failure to respond to bisphosphonates is extremely rare in Paget's disease, though it may occur. In these cases adding calcitonin may sometimes induce remission.

Etidronate has been most widely used for Paget's disease and is currently the only bisphosphonate licensed in Britain for treating this condition. It is generally given at a dose of 5-10 mg/kg daily for six months. But even at these comparatively low doses focal osteomalacia may occur with the development of pathological fractures in some cases.[24] An alternative approach that has been advocated is to use higher doses for shorter periods. The response in terms of a reduction in serum alkaline phosphatase activity is of the order of 40-60% with either regimen; this is associated with a good clinical response in most patients.

More potent antiresorptive bisphosphonates are currently being evaluated in Paget's disease. Of these,

pamidronate and clodronate have been most extensively studied, though tiludronate, risendronate, and alendronate have all been shown to suppress serum alkaline phosphatase activity by between 40% and 70%. Pamidronate is available only for intravenous use in Britain. The optimal regimen in Paget's disease has not been defined. Oral administration of 250-500 mg daily for three to six months produces 60-70% suppression of serum alkaline phosphatase activity. Intravenous regimens produce similar effects—for example, 15 mg daily for five days, 30 mg weekly for six or 12 weeks, 45 mg every three months for one year, and a single intravenous infusion of 60-105 mg. However, histological changes indicating impaired mineralisation have been reported after intermittent intravenous pamidronate.[25] No adverse clinical effects have been reported, but further evaluation of the relevance of these findings is required.

Clodronate is available in Britain for oral and intravenous use, though like pamidronate it is not licensed for the treatment of Paget's disease. Oral doses of 800-1600 mg daily for one to six months produce effective suppression of disease. Alternatively a five day course of daily intravenous injections of 300 mg produces comparable clinical and biochemical improvement.

HYPERCALCAEMIA ASSOCIATED WITH MALIGNANCY

Hypercalcaemia of malignancy may result from the release of systemic or local factors, or both, from tumours or from invasion of bone by the tumour itself.[26] The resulting increase in bone resorption leads to hypercalcaemia, which is often compounded by reduction in the capacity of the kidneys to excrete calcium. This kidney impairment is multifactorial, reduced glomerular filtration rate and (in cases associated with production of parathyroid hormone related peptide) increased tubular reabsorption of calcium being particularly dominant. Ideally, treatment should be aimed at the primary tumour but often this is impossible. Successful management of hypercalcaemia, however, produces worthwhile clinical results in most patients and is based on rehydration and suppression of bone resorption.

Bisphosphonates produce the most consistent, rapid, and effective treatment of hypercalcaemia associated with malignancy.[23,27] In Britain etidronate, clodronate, and pamidronate are licensed for this indication. Because of the nausea and vomiting often associated with hypercalcaemia, intravenous administration is generally preferred, though oral treatment may be substituted later. Based on criteria of consistency and speed of response, pamidronate and clodronate are more effective than etidronate. However, when hypercalcaemia is predominantly due to increased renal tubular reabsorption of calcium, as in humoral hypercalcaemia of malignancy, the response to bisphosphonates may be absent or incomplete.

Bisphosphonates in hypercalcaemia of malignancy

- Bisphosphonates provide the most consistent, rapid, and effective treatment of hypercalcaemia of malignancy. Etidronate, pamidronate, and clodronate are licensed for use in this condition in Britain
- The response to pamidronate and clodronate occurs within 48 hours, and normocalcaemia is usually achieved within one week. With etidronate hypercalcaemia usually recurs within a few weeks
- In cases associated with secretion of parathyroid hormone related peptide and increased renal tubular reabsorption of calcium the response to bisphosphonates may be incomplete or absent

Pamidronate is most commonly given as a single infusion in doses of 30-45 mg at a rate of 7·5-15 mg hourly. Alternatively it may be given in divided doses over two to four days with a maximum of 90 mg for each course. More rapid rates of infusion should be avoided, as they may result in deterioration of renal function. A response is usually seen within 48 hours, normocalcaemia being achieved within one week. The duration of remission is variable but in most cases hypercalcaemia recurs within a few weeks. Clodronate is also given by slow intravenous infusion, the recommended dose being 300 mg daily for 7-10 days or a single dose infusion of 1·5 g over four hours. Etidronate is less effective in severe hypercalcaemia, particularly when non-metastatic in origin, but can be given intravenously in doses of 7·5 mg/kg for three days, repeated if necessary after seven days or longer.

Alendronate, though not yet available in Britain for clinical use, shows promise in malignant hyercalcaemia, doses of 5-10 mg infused over two or more hours being effective initially; thereafter, weekly infusions of 2·5 mg maintain normocalcaemia. Tiludronate also restores normocalcaemia in this condition but the doses required are associated with a high risk of nephrotoxicity.

Interactions and side effects

Reduced intestinal absorption of calcium, iron, and antacids occurs with concurrent administration of bisphosphonates. When coprescription is necessary these drugs should always be taken at least two hours apart from the bisphosphonate. Severe hypocalcaemia has been reported in patients taking aminoglycosides and bisphosphonates.

Gastrointestinal side effects, particularly nausea and diarrhoea, sometimes occur with oral bisphosphonate, and the aminobisphosphonates—for example, pamidronate—may cause transient fever with leucopenia and increased C reactive protein. Rapid intravenous administration may lead to renal failure, possibly as a result of formation of insoluble calcium bisphosphonate complexes in the blood. Asymptomatic hypocalcaemia may occur with bisphosphonate, and hyperphosphataemia has been described in association with etidronate as a result of inhibition of renal tubular reabsorption. A few cases of acute leukaemia have been described in patients receiving clodronate but a direct causal association has not been established. Occasional skin reactions have also been described in patients receiving clodronate.

Inhibition of mineralisation

The ability of bisphosphonates to inhibit mineralisation varies between compounds and is unrelated to antiresorptive potency. When used in Paget's disease etidronate has been reported to cause focal osteomalacia and pathological fracture in doses as low as 5-8 mg/kg daily, the risk and severity of this complication increasing with dosage.[24] The effects on mineralisation of long term intermittent etidronate for osteoporosis have been studied in comparatively few patients. No increase in mean osteoid seam width has been reported after two to six years of treatment, but in one study an increase in mineralisation lag time was seen after 60 weeks (median 120 *v* 47 days), normal values being obtained after three years.[5] The known ability of low doses of etidronate to impair mineralisation together with the long duration of treatment required for osteoporosis and the long half life of bisphosphonates in bone raise concerns that osteomalacia may occur as a late complication of etidronate given for osteoporosis. Further studies are required to resolve this important question.

Toxicity of bisphosphonates

- Bisphosphonates have low toxicity, gastrointestinal side effects occurring in a few patients. Rapid intravenous administration of bisphosphonates may cause renal failure, and administration of aminobisphosphonates is sometimes associated with transient fever and leucopenia
- Long term side effects of potential concern include defective mineralisation of bone and low bone turnover, both of which may adversely affect bone strength. The frequency and severity of these effects vary with different bisphosphonates

There are few data concerning the effects of other bisphosphonates on mineralisation in human bone. However, in general they produce little or no inhibition of mineralisation at doses which show antiresorptive activity. Recently, increased osteoid seam width, indicating reduced mineralisation, has been reported in patients with Paget's disease given intravenous pamidronate, either 30 mg once weekly for six weeks or 45 mg every three months for one year.[25] No fractures were reported in these patients and mineral appositional rates were not suppressed to subnormal. Nevertheless, these findings indicate that these doses of pamidronate may have adverse effects on mineralisation.

Reduction of bone turnover

Suppression of bone turnover, though producing beneficial effects on bone mass in high turnover osteoporosis, may have long term adverse effects. Low bone turnover is associated with an increase in bone age and impaired microdamage repair, changes which are likely to reduce the mechanical integrity of bone. The long term effects of bisphosphonates on activation frequency have been investigated in two studies. Storm *et al* reported that values after three years of treatment were similar to those at baseline, suggesting that the previously increased activation frequency was returned to normal by treatment (fig 4).[5] In another study,

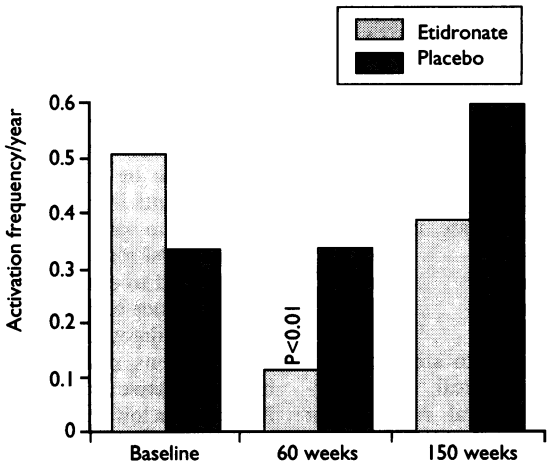

FIG 4—*Effects of intermittent cyclic etidronate on activation frequency in iliac crest bone from women being treated for postmenopausal osteoporosis. In treatment group there was significant reduction in activation frequency after 60 weeks with return to near baseline at 150 weeks. (From Storm et al[5])*

however, activation frequency was suppressed to well below baseline after two years of cyclic intermittent etidronate.[6]

Conclusions

The development of bisphosphonates represents a major therapeutic advance and they are now the treatment of choice in Paget's disease and malignant hypercalcaemia. Bisphosphonates also show considerable promise in the prevention and treatment of osteoporosis. Evaluation in postmenopausal and corticosteroid induced osteoporosis has shown beneficial effects on bone mass, particularly in the spine, though a reduction in fracture rate remains to be firmly established.

The long half life of bisphosphonates in bone provides a rational basis for intermittent treatment in all these conditions, but optimal regimens for Paget's disease and osteoporosis have yet to be established; and in osteoporosis the need for calcium supplementation is unproved. Adverse effects on mineralisation, at least for some bisphosphonates, are a cause for potential concern, and in patients with osteoporosis long term effects on bone turnover require more thorough documentation. Overall, however, bisphosphonates are well tolerated and safe and the outcome of clinical trials which address the issue of fracture in osteoporosis is eagerly awaited.

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