

Bisphosphonates in osteoporosis: Where do we stand in 2009?

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Abstract

Bisphosphonates were discovered 40 years ago and remain the market leader in the field of osteoporosis. Bisphosphonates are classified as inhibitors of bone resorption and they act by inhibiting the mevalonate pathway to inhibit protein prenylation with resultant inhibition of osteoclastic activity. There are three ethical bisphosphonates as well as generic alendronate that have been approved for the treatment of osteoporosis in South Africa. These drugs offer a wide range of variations in dose, frequency of administration and method of administration. The wide choice in method of administration may lead to improved individual compliance to treatment protocols. There is strong evidence to support antifracture efficacy at vertebral and hip sites in patients treated for up to three years but long-term data as well as prospective data in osteopenic patients are lacking. Gastrointestinal side-effects are common, but can often be avoided by taking medication in the prescribed fashion. The acute phase response to intravenous administration can be prevented by co-administration of oral paracetamol or ibuprofen. Bisphosphonates can cause bone pain. The Food and Drug Administration (FDA) has accepted evidence that bisphosphonates do not cause atrial fibrillation. Osteonecrosis of the jaw is a rare complication of oral bisphosphonates as used in osteoporosis but may be associated with high dose intravenous treatment in cancer patients. Atypical low energy femur shaft fractures have been associated with long-term usage of the bisphosphonates. A large national observational register-based study reported that these fractures share the same epidemiology and treatment response as classical hip fractures and are best classified as osteoporotic fractures. The cost-effectiveness and treatment options of the bisphosphonates will ensure that they remain significant players in years to come.

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Historical introduction

The development of the bisphosphonates from the preclinical stage to the most commonly used pharmaceutical compound for the prevention and treatment of osteoporosis-related fractures, is intimately linked to the person of Herbert Fleisch, late Swiss physician and scientist. His group found that plasma and urine contained inorganic pyrophosphate that inhibited calcium phosphate precipitation. Pyrophosphate had at that time been used industrially as an additive to washing powders to prevent the deposition of calcium carbonate in pipes. Pyrophosphate had limited clinical application as a result of rapid hydrolysis after oral administration. This led to the discovery of the bisphosphonates about 40 years ago. The bisphosphonates were shown to resist enzymatic hydrolysis and inhibit bone resorption.¹ Since 1980 various new bisphosphonates have been developed. These drugs judged by the standards of evidence-based medicine were required to prove antifracture efficacy in large randomised placebo-controlled trials. Alendronate, risedronate, zoledronic acid and alendronate generic compounds are registered in South Africa for the prevention and treatment of osteoporosis-related fractures. The present discussion will be limited to these drugs. Collectively they represent in excess of 80% of the drugs used in this market segment. As with most drugs, utility is limited by various undesired side-effects. Recent concerns have been expressed regarding the long-term effect of the bisphosphonates on bone quality and bone strength. The aim of this article is to evaluate the present role of bisphosphonates in osteoporosis, taking into account strengths and weaknesses.

Chemistry and pharmacokinetics

The bisphosphonates are synthetic compounds derived from pyrophosphate, characterised by a P-C-P bond that is resistant to chemical and enzymatic hydrolysis. The basic P-C-P structure can be modified at the two lateral chains on the carbon atom or by esterifying the phosphate groups, leading to unique members of the family with distinct effects on bone metabolism. The ability of the compound to bind to bone surface seems to be dependent on the P-C-P bond while the side chain in combination with the P-C-P bond defines ability to inhibit bone resorption. The pharmacokinetic profile of oral alendronate has been studied extensively. Bisphosphonates are poorly absorbed, especially so in the presence of food or calcium. It is estimated that less than 1% of alendronate is absorbed. This mainly occurs in the stomach by passive diffusion. Within hours of ingestion, 50% of the absorbed dose is excreted in the urine and 50% is deposited in bone. This happens rapidly resulting in a very short plasma half-life. The absorbed alendronate is buried under new layers of bone but will be released again when that area in which the alendronate is deposited is resorbed. The rate at which this occurs is determined by the rate of bone turnover. It is estimated that the total accumulation of alendronate after 10 years of standard dosing (10 mg daily) is 75 gram. If administration is stopped after 10 years, bone remodelling will still result in skeletal release of alendronate equivalent to a daily oral dose of 2.5 mg.

Mode of action

The bisphosphonates belong to the class of antiresorptive drugs. The ability of the bisphosphonates to inhibit osteoclast-induced bone resorption, to slow down bone turnover and to increase bone mass leads to an overall increase in bone strength that is reflected in antifracture efficacy in various clinical trials. Bisphosphonates reduce osteoclast numbers by the inhibition of recruitment of pre-osteoclasts and by the activation of apoptosis. Osteoclastic activity is inhibited. There is good evidence that the nitrogen-containing bisphosphonates inhibit the mevalonate pathway to inhibit protein prenylation. The effects of bisphosphonates on the osteoblast may include suppression of bone formation, especially after long-term use. The clinical relevance of this will be discussed later.

Strengths

Proof of efficacy

The nitrogen-containing bisphosphonates alendronate, risedronate and zoledronic acid have collectively been subjected to extensive randomised controlled clinical trials. Registration requires three years of treatment follow-up. All three drugs showed significant fracture protection against morphometric and clinical vertebral fracture² as well as hip fracture.³ In terms of non-vertebral fractures, risedronate and zoledronic acid offered significant protection in primary analysis,⁴ whereas the antifracture efficacy of alendronate in this subset was only significant in pooled analyses of FIT 1 and 2 studies.⁵ No head-to-head studies comparing the antifracture efficacy of these drugs to each other or to other treatment modalities have been done.

Variable mode of administration

Lack of compliance with medication is a reason for concern in the field of osteoporosis.⁶ The bisphosphonates offer variable modes of administration including variable oral and intravenous regimens that may increase compliance.

Cost

In South Africa, the cost of the originator, alendronate, has recently been lowered considerably. This was prompted by the availability of various cheaper generic alendronate. Concern has been expressed about the lack of proven clinical efficacy of the generic alendronate.⁷ A recent German study found original branded alendronate and risedronate to be significantly superior to the generics after one year in respect of bone mineral density (BMD). This may have been related to a higher incidence of gastrointestinal adverse events in the generic group, resulting in lower compliance.⁸

Weaknesses

Lack of long-term fracture data

Proof of efficacy as regards fracture protection for longer than three years with bisphosphonates, is not as convincing as the three year data. A total of 247 patients on alendronate 10 mg daily were followed-up for 10 years.⁹ The primary endpoint was the change in BMD at the lumbar spine. Data on vertebral and clinical fracture were collected as safety endpoints. A mean increase in lumbar spine BMD of 13.7% ($p < 0.001$) versus baseline and a mean increase in trochanter hip BMD of 10.3% ($p < 0.001$) versus baseline were recorded. It was concluded that continuous treatment with alendronate 10 mg daily for 10 years sustained therapeutic effects on BMD and bone remodelling, with no lessening of antifracture efficacy over time. These conclusions should be interpreted with caution, considering the significant limitations of the study, especially regarding the ability of the study to monitor sustained fracture efficacy. A total of 136 patients completed risedronate therapy

over seven years. The interpretation of the study is limited by the lack of a placebo group and small numbers.¹⁰ Data on zoledronic acid is limited to three years, but currently a three year extension is ongoing.

Lack of data in osteopenic patients

Treatment in osteoporosis has generally been directed at the patient with osteoporosis as defined by a BMD DXA T-score of < -2.5 . It is now accepted that patients at risk of fracture, based on a combination of risk factors, such as incorporated in the FRAX model, should also be targeted for therapy.¹¹ This implies that some patients with a BMD T-score of between -1.0 and -2.5 (osteopenia) may be considered for treatment. It is thus important to note that all trials involving the bisphosphonates and that have proven antifracture efficacy had excluded osteopenic patients or the data was adjusted post hoc to only include patients at a BMD of < -2.5 . A post hoc subgroup analysis on risedronate, that pooled data from four different studies, claims efficacy for vertebral fracture protection in patients with osteopenia at the hip without vertebral fracture.¹² It should be noted that in a randomised controlled trial risedronate failed to protect against hip fracture in the absence of hip BMD T-score < -3.5 .

Side-effects

Gastrointestinal side-effects

Gastrointestinal side-effects such as nausea, vomiting, dyspepsia, gastric pain, diarrhoea and oesophageal erosions after the administration of standard dose oral bisphosphonates, are the most common side-effects reported by patients and are a significant reason for discontinuation of medication. The exact mechanism of action remains unknown, but the majority of oesophageal adverse events can be prevented by taking the drug with a full glass of water and by remaining upright and fasting for the next 30 minutes. The ability of oral bisphosphonate to irritate the gastrointestinal system has recently been highlighted by a report of 23 cases of oesophageal carcinoma in the USA in patients on oral bisphosphonates. Although no direct causal relationship has been established, it is recommended that caution be applied and that such therapy not be used in patients with Barrett oesophagus.¹³ Less frequent dosing schedules, such as weekly or monthly, although at higher doses than daily, seem to have less gastric side-effects and to be better tolerated by patients.

Acute phase reaction after intravenous infusion

All bisphosphonates, when administered as an intravenous infusion, may result in transient post-infusion symptoms similar to those associated with mild influenza, including fever, myalgia, arthralgia, headache and nausea. These symptoms usually occur within 72 hours after the infusion and are mild-to-moderate in severity, generally resolve within one to four days and are much less likely to occur after later doses than after the first infusion. The mechanism underlying these symptoms is poorly understood. A recent study concluded that oral paracetamol or ibuprofen is effective in managing the transient flu-like symptoms associated with the administration of zoledronic acid IV and recommended that one of these agents be administered four hours after zoledronic acid infusion, particularly among bisphosphonate-naïve patients.¹⁴

Bone pain

Bone pain associated with the use of bisphosphonates is a side-effect often overlooked by physicians. The FDA in 2008 alerted physicians to the fact that some patients taking bisphosphonates may experience musculoskeletal pain within days, months or even years after initiating therapy. The pain may subside after discontinuation of the drug. The mechanism of action, incidence and predisposing factors are presently unknown.

Atrial fibrillation

A possible relationship between atrial fibrillation reported as a serious adverse event and the use of zoledronic acid 5 mg IV was reported by Black.¹⁵ It should be noted that the incidence of all reported events of atrial fibrillation was not significantly different between placebo and treated groups. The FDA, after reviewing the data of 19 687 patients treated with bisphosphonates and 18 358 patients on placebo, ruled that no clear association between the use of bisphosphonates and cardiac arrhythmias was apparent and advised that physicians should not alter present prescribing practices.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a rare condition characterised by necrotic exposed bone in the maxillofacial region. An association between the use of bisphosphonates and ONJ has been postulated for a few years and has caused much concern, especially amongst dentists. Most cases have been reported in patients with malignancies such as multiple myeloma or breast cancer treated with high doses of bisphosphonate therapy intravenously. It has rarely been reported in patients with postmenopausal osteoporosis or Paget disease of bone treated with standard doses of bisphosphonate therapy. Other predisposing factors are associated corticosteroid therapy, chemotherapy, head and neck irradiation, trauma, poor dental hygiene and dental surgery. A recent critical review of the literature reported that the aetiology of ONJ remains unknown and that to date no direct causal link to bisphosphonates has been established.¹⁶ Various bodies have developed guidelines for the prevention of ONJ. The Canadian guidelines recommend that in all oncology patients considered for bisphosphonate treatment a thorough dental examination including radiographs be completed prior to initiation of treatment. Any invasive treatment needs to be completed prior to therapy.¹⁷ Although much remains to be learned about this condition, including its true incidence in various patient populations, evidence to date suggests that ONJ poses a very small potential risk to the generally healthy patient being treated for osteoporosis in normal recommended doses.

Low energy subtrochanteric femur fractures

Odvina et al first reported concerns about potential over-suppression of bone turnover during long-term use of bisphosphonates. They reported on nine patients who sustained spontaneous non-vertebral fractures while on alendronate therapy, six of whom displayed either delayed or absent fracture healing for three months to two years during therapy. Histomorphometric analysis of the trabecular bone showed markedly suppressed bone formation in most patients.¹⁸ This report was followed by more cases that had several features in common. After a few years of bisphosphonate use (mostly alendronate) the patients presented with fractures of the femur shaft in the subtrochanteric region after minimal trauma. The fractures are sometimes preceded by bone pain. The first fracture is often followed by a subsequent fracture in the contra lateral femur. X-rays have a common pattern characterised by a simple transverse fracture line and hypertrophy of the diaphyseal cortex. This may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair resulting from its prolonged use of bisphosphonates. It has been speculated that long-term bisphosphonate therapy may increase the risk of unusual long bone mid-shaft fractures due to prolonged suppression of bone turnover, which could lead to accumulation of microdamage and development of hypermineralised bone. At present, the scope of this complication in the larger context of patients receiving bisphosphonate therapy is not known, but appears to be small. In a large national observational register-based study, Abrahamsen et al reported that subtrochanteric femur fractures share the same epidemiology and

treatment response of classical hip fractures and are best classified as osteoporotic fractures.¹⁹

The need for a drug holiday

The possibility of over-suppression of bone turnover and the possible risk of ONJ and low energy femur shaft fractures during extended usage has raised the question of how long bisphosphonate therapy should be continued. This question becomes even more relevant when considering the fact that bisphosphonates have the unique ability to accumulate in the skeleton. The only evidence to base any recommendation on is a study that compared the effects of discontinuing alendronate treatment after five years with continuing for ten years. Women who discontinued alendronate after five years showed a moderate decline in BMD and a gradual rise in biochemical markers but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to five years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond five years.²⁰ The design of this trial is unfortunately not robust enough to be definitive on the subject. Every clinician will have to decide in the individual patient on when to stop treatment or when to switch to other medication. The use of anabolic medication such as parathyroid hormone or a dual action agent such as strontium ranelate could be considered after five years of bisphosphonate treatment in a patient still at risk of fracture.

Conclusion

It is a remarkable feat that the bisphosphonates are market leaders in the field of osteoporosis, forty years after discovery. This is testimony of the considerable strengths of the bisphosphonates. It is unlikely that any of the possible side-effects as discussed will have a major impact on the utility of the bisphosphonates in the near future. A main driver of the future use of bisphosphonates will be cost-effectiveness.

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