



Bisphosphonates in osteoporosis

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The clinical effects observed with bisphosphonates include an increase in bone mineral density and an increase or improvement in bone strength as well as a decrease in the risk of bone fracture.¹

Bisphosphonates suppress osteoclast activity, which results in the inhibition of bone resorption.² Due to their inhibitory effect on bone resorption, they decrease bone loss and preserve bone mass.¹ As a result, bone density is increased, bone turnover decreased and the risk of fractures is therefore reduced.^{1,2}

Mode of action

Bisphosphonates are potent inhibitors of osteoclastic bone resorption.³ They are attracted to the hydroxyapatite, which is the major calcium-containing mineral in bone.⁴ They bind avidly to bony surfaces where mineral is exposed (at the site of bone resorption).^{3,5}

The bone-impregnated bisphosphonates are released when osteoclasts resorb bone and, once released, the bisphosphonate impairs the ability of the osteoclast to attach to the bony surface.¹ Bisphosphonates therefore interfere with a step in bone metabolism that is essential for continued bone resorption.⁵ They also promote osteoclast cell death (apoptosis) by reducing osteoclast activity.¹

Bisphosphonates can be divided into two groups, simple bisphosphonates and those with a nitrogen-group and they have different mechanisms of action.

- Nitrogen-containing bisphosphonates are thought to suppress osteoclast activity by binding to and suppressing the enzyme farnesyl pyrophosphate synthase.⁴ This creates abnormalities in the osteoclast, which promotes the detachment of the osteoclast from the bone and results in the reduction of bone resorption.^{1,6}
- Simple bisphosphonates are metabolised to cytotoxic adenosine triphosphate analogues which are incorporated into osteoclasts.^{1,4} This results in the formation of osteoclasts that undergo apoptosis or programmed cell death.^{1,6}

It is thought that bisphosphonates also have an effect on osteoblasts. However, the mode of action is still unclear and there is no consensus on the effect(s) of bisphosphonates on osteoblasts.⁵

Despite similarities, bisphosphonates differ in potency, duration of action and toxicity.^{5,6} Compared to simple bisphosphonates, those containing a nitrogen-group are more potent inhibitors of bone resorption (Table I).⁶ There is a direct correlation between the relative antiresorptive potency of nitrogen-containing bisphosphonates and the potency with which they inhibit the enzyme farnesyl pyrophosphate synthase.⁶

Table I. Bisphosphonates according to potency in inhibiting bone resorption⁵

Amino- or nitrogen-containing bisphosphonates:		Increasing potency
Zoledronic acid (zoledronate)* (> 10 000 x)		
Risedronate* (1 000 – 10 000 x)		
Ibandronate* (1 000 – 10 000 x)		
Neridronate		
Alendronate* (100 – 1 000 x)		
Pamidronate* (~100 X)		
Simple bisphosphonates or non-aminobisphosphonates		
Clodronate* (~10 x)		
Tiludronate		
Etidronate (~1 x)		

*Available in South Africa⁵

Another factor that contributes to the potency and duration of action of bisphosphonates is their ability to adsorb to bone mineral (Table II). This may be the reason for zoledronate's and alendronate's seemingly prolonged clinical duration of action.⁵

Table II. Bisphosphonates according to their ability to adsorb to bone mineral

Zoledronate		Increasing potency
Alendronate		
Ibandronate		
Risedronate		
Etidronate		
Clodronate		

Indications

Bisphosphonates are widely used and they are considered forerunners in the treatment of metabolic bone diseases associated with an increase in bone resorption.^{5,6}

The main indications for the use of bisphosphonates include:

- Osteoporosis (postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis [GIOP])^{1,5,6}
- Hypercalcaemia such as tumour-induced hypercalcaemia^{1,6}
- Metastatic bone disease, myeloma^{1,5,6}
- Paget's disease of bone^{5,6}

Pharmacokinetics

In general, gastrointestinal absorption of oral doses is poor; less than 1% of an oral dose is absorbed.^{1,2,5} Approximately half of the absorbed dose is bound to bone mineral and the remainder excreted via the kidneys.^{1,6} Bisphosphonates are not metabolised and have a high renal clearance.⁵

Since bisphosphonates bind with a high affinity and are incorporated into newly formed bone, their action persists for a long time after the treatment has stopped (elimination half-life ≥ 10 years).^{1,3,5}

Efficacy

Osteoporosis

An improvement in bone mineral density (BMD) has been observed with the use of ibandronate, risedronate and zoledronate in postmenopausal women with osteoporosis.² Bisphosphonates are considered first-line treatment for osteoporosis in women, men and for the treatment of secondary osteoporosis such as GIOP.⁵

A marked suppression of bone turnover and an increase of 2–10% in bone mineral density (BMD) has been observed with the bisphosphonates.⁵ More than 30 randomised controlled trials have documented the antifracture efficacy of bisphosphonates in the treatment of osteoporosis.⁵ Over a period of three years, the relative risk of vertebral fractures was generally reduced by approximately 40–50% and that of non-vertebral fractures by approximately 25–35%.⁵ However, data on sustained antifracture efficacy beyond four years is not conclusive.⁵

The antifracture effect of bisphosphonates in patients with osteopenia is unclear since antifracture studies have been limited to patients with a BMD in the osteoporosis range or in those who had prior fractures (i.e. patients with a high-risk of fractures).⁵

According to the South African guidelines from the National Osteoporosis Foundation of South Africa (NOFSA), bisphosphonates should be reserved for patients with a BMD T-score $\leq -2,5$ and/or prior fracture.⁵

In South Africa, the following bisphosphonate-containing products are indicated for the treatment of osteoporosis:

- Oral alendronate tablets are available for either daily (10 mg) or weekly (70 mg) dosing.⁵ Some products may also contain Vitamin D (cholecalciferol).⁷
- Risedronate is available as weekly or monthly tablets.⁵ Risedronate 35 mg tablets are recommended once a week on the same day each week and the 150 mg tablet should be taken once a month.^{3,7}
- Ibandronate is available as monthly tablets (150 mg once a month)^{7,8} and as a three-monthly intravenous injection (3 mg IVI over 15–30 seconds every three months).^{7,8}
- Zoledronate is available as an annual intravenous infusion (5 mg as a single dose administered over at least 15 minutes once a year).^{3,5}

An alternative bone active treatment should be considered for patients:

- With fractures or BMD that is still in the osteoporosis range (T-score $\leq -2,5$)⁵ or
- With ongoing risk factors or
- Whose BMD responded poorly whilst on treatment⁵

Safety

In general, bisphosphonates are well-tolerated.⁵ Side-effects may differ, depending on the route of administration i.e. oral versus intravenous.

Adverse events specific to the route of administration

Oral bisphosphonates

Upper gastrointestinal (GI) discomfort is a common side-effect with oral bisphosphonate preparations and includes symptoms such as nausea, vomiting, heartburn and chest pain.⁵ The risk of these side-effects is higher in patients who recline within 30–60 minutes after taking a bisphosphonate.⁵ In addition, daily dosing of bisphosphonates is more likely to cause GI side-effects than weekly or monthly dosing.⁵

Intravenous bisphosphonates

A transient flu-like syndrome (pyrexia, muscle pain, headache and nausea) has been reported in 15–45% of patients, following intravenous (IV) administration of bisphosphonates. The flu-like syndrome may occasionally be prolonged. It is usually seen with the first dose and symptoms generally subside within a few days.^{1,5} Large doses given IV may cause hypocalcaemia, especially in children.⁵

Musculoskeletal pain

There have been occasional reports of incapacitating bone, joint, and/or muscle pain from patients receiving bisphosphonates. The time of onset varies; symptoms may occur within days, months, or years after starting a bisphosphonate (usually starts about three months after treatment was initiated).⁹ In most patients, musculoskeletal pain improved following discontinuation. However, it does not always resolve completely.⁹

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a rare complication of bisphosphonate therapy. With oral bisphosphonate doses used in the treatment of osteoporosis, the incidence is extremely low (0,01–0,0004%).^{5,10} ONJ has mainly been reported in patients with underlying malignancies or those using doses of intravenous bisphosphonates which are 10-fold higher than those used in the treatment of osteoporosis.⁵ The majority of cases have also occurred following invasive dental procedures.³

Atypical fragility fractures

Atypical fragility fractures (AFF) are another rare complication of bisphosphonates (higher incidence with alendronate). It is associated with chronic (longer than five to ten years), use of bisphosphonates.^{3,5} The causal relationship has, however, not been established.⁵

AFF usually occur in areas rich in cortical bone (e.g. subtrochanteric or diaphyseal femur, pelvic bones) and arise with minimal or no trauma, and may be bilateral.^{5,10} Early symptoms include pain and tenderness over the immediate fracture site (femur shaft) as well as discomfort, weakness or pain in the thigh, hip or groin area.^{1,10}

Dosing

Dosing of bisphosphonates would depend on the active ingredient and the strength of the formulation. Daily, weekly and monthly oral dose regimens are available.

Intravenous preparations may be a more suitable option for patients who are unable to sit upright for 30–60 minutes after taking an oral preparation, for those who cannot tolerate oral regimens or for patients on long-term treatment for metabolic bone disease.¹

Duration of treatment

Bisphosphonate-treatment should be reassessed after five years of treatment.³ The South African guideline (NOFSA) suggests a 'drug holiday' may be considered after five years of treatment for patients who are not at very high fracture risk, especially for those with GIOP.⁵

The guidelines do not have any recommendations regarding the duration of the 'drug holiday' and the length should be determined upon individual assessment.¹ Following discontinuation of bisphosphonates, BMD is usually maintained. However, patients should be monitored for any new fractures and accelerated bone loss after 18–24 months.⁵

Drug interactions

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the likelihood of upper GI events and should therefore be avoided or used with caution in patients who are using oral bisphosphonates.^{1,9}

Antacids or vitamin or mineral supplements containing multivalent cations (e.g. aluminum, calcium, magnesium, iron) may decrease the absorption of oral bisphosphonates when taken concomitantly.⁹ Oral bisphosphonates should be administered at least 60 minutes (or depending on bisphosphonate up to two hours) prior to taking any other oral medication or supplement.⁹

Caution is advised with concomitant use of loop diuretics (may cause hypocalcaemia), aminoglycoside (may have a possible additive effect in lowering serum calcium concentrations for prolonged periods) and nephrotoxic agents (may increase the risk of renal dysfunction) with zoledronic acid.⁹

Contraindications, special warnings and precautions for use

Severe adverse oesophageal effects including oesophagitis, oesophageal ulcers, and/or erosions (occasionally with bleeding and rarely followed by oesophageal stricture or perforation) have been reported in patients receiving oral bisphosphonates.⁹ Oral bisphosphonates should therefore not be prescribed for patients with known upper-gastrointestinal disease or in patients who are unable to stand or sit upright for at least 30 minutes after taking an oral bisphosphonate.⁵

Bisphosphonates are contraindicated in pregnancy (bisphosphonates cross the placenta and studies in pregnancy are limited) and in breastfeeding.^{3,5} The use of bisphosphonates is also not recommended for patients with:

- Known hypersensitivity to the bisphosphonate or any ingredient in the formulation⁹
- A creatinine clearance < 30 ml/minute⁵
- Hypocalcaemia – Before initiating treatment hypocalcaemia should be corrected⁹

Important prescribing points

Administration-related

Intravenous formulations

- High doses of intravenous formulations given via rapid infusion may cause formation of insoluble aggregates in the circulation, which may impair renal function or precipitate renal failure.⁵ IV products should be administered via slow infusion.⁵
- Patients receiving intravenous bisphosphonates should be warned about the possibility of developing a transient flu-like syndrome.^{5,10} This syndrome usually responds well to NSAIDs or paracetamol.¹⁰

Oral formulations

Oral bisphosphonates are best absorbed when taken on an empty stomach. Absorption is decreased in the presence of food, calcium, tea or coffee and juice.⁶

- It is therefore recommended that patients should take bisphosphonates :
 - First thing in the morning after waking.

- With a glass of tap water on an empty stomach.⁵
- In order to minimise the risk of gastrointestinal ulceration or gastrointestinal side-effects, patients should swallow tablets whole, without chewing or sucking.⁹
- After taking oral bisphosphonates patients should:
 - wait for at least 30 minutes before eating any food, drinking any liquids other than tap water or taking other medication. Calcium-containing products or antacids should be taken at least two hours apart from bisphosphonates;¹
 - not lie down for 30–60 minutes.⁵

Patients treated with bisphosphonates should also receive adequate calcium and vitamin D based on individual needs.³

Safety related

Although it is not routinely recommended for the patient to have a dental examination prior to starting a bisphosphonate, if major dental surgery is anticipated, it may be prudent to complete the procedures before initiating bisphosphonate treatment.⁵

Patients should practice good oral hygiene, have regular dental check-ups and, as a precaution, patients should inform their dentist if they are using bisphosphonates.^{3,5}

Patients treated with bisphosphonates should be advised to promptly contact their doctor if they develop:

- Severe bone, joint, or muscle pain⁹ or
- New thigh or groin pain⁹
- Dysphagia, retrosternal pain or local irritation of the upper gastrointestinal tract.³

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