

Adverse effects of bisphosphonates

Introduction:

Bisphosphonates inhibit the bone resorption part of the continual cycle of bone resorption and regrowth. They are a useful group of drugs for the treatment of hypercalcaemia, bone metastases, osteoporosis, and Paget's disease. However, they have a wide range of adverse effects, some of which may be severe.

The bisphosphonates currently available in New Zealand are etidronate (oral), alendronate (oral), pamidronate (intravenous) and zoledronic acid (intravenous).

Alendronate, pamidronate, and zoledronic acid are all nitrogen-containing bisphosphonates, in contrast to etidronate, which is not. The nitrogen-containing bisphosphonates are more potent inhibitors of bone resorption than etidronate.

Pharmacokinetics and dosing:

Bisphosphonates are poorly absorbed orally and absorption is optimised when taken on an empty stomach (1-5% of an oral dose is absorbed in the fasting state). Absorption of bisphosphonates can be reduced by the presence of food, some medication and beverages in the stomach. Approximately 80% of the absorbed bisphosphonate is renally cleared, with the remaining 20% being taken up by bone. The plasma half-life is approximately one hour, while the bisphosphonate may persist in bone for the lifetime of the patient.

To minimise the risk of tablets getting lodged in the oesophagus, it is recommended that the oral drugs be taken with a full glass of water upon rising for the day. It is important that the patient does not lie down for at least 30 minutes after taking their dose and until after their first meal of the day.

Adverse effects:

Upper GI side effects such as oesophagitis and oesophageal erosion are common with oral bisphosphonate use and often lead to premature cessation of treatment, even when taken correctly. Non-nitrogen containing bisphosphonates eg. etidronate, produce fewer upper GI adverse effects but more diarrhoea compared to alendronate.

Acute phase reactions with intravenous bisphosphonates are described as 'flu-like' and consist of fever, myalgia, fatigue and often bone pain. Symptoms are usually self-limiting and generally resolve over hours to a few days after administration. Symptomatic treatment with simple analgesics/antipyretics is often helpful. This reaction is often more pronounced after the first infusion than with subsequent doses.

Bone, muscle and joint pain have all been reported separately to the acute-phase reaction, after a median time of 14 days. The majority of patients who experience this complain of muscle and bone pain combined with fatigue, while isolated bone or joint pain is relatively rare. This is a poorly understood side effect which may be underreported. A strategy of pause and rechallenge is feasible in mild cases.

Atypical femoral fragility fractures have been rarely reported among patients using oral bisphosphonates (usually alendronate). Case reports indicate that patients with such fractures have low-normal bone turnover, with fractures occurring after little or no trauma. They are associated with characteristic radiological features, delayed healing, bilateral hip signs and symptoms, and sometimes prodromal thigh pain preceding the fracture for weeks to months.

Bisphosphonate-induced osteonecrosis of the jaw is a particularly interesting adverse effect. It ranges from mild self-limiting cases to severe cases needing reconstructive surgery. The jaw is believed to be a site of particularly high bone turnover, and thus a site with large amounts of bisphosphonate deposition. Osteonecrosis is more common with the more potent bisphosphonates, and in patients receiving frequent infusions eg. in oncology as opposed to those taking oral compounds for osteoporosis.

Kidney damage has been associated with intravenous bisphosphonates. It is much less clear if this is a concern in patients who take oral bisphosphonates.

Ocular adverse effects such as uveitis, periscleritis and scleritis are rare side effects of bisphosphonate therapy. Symptoms often occur after an acute phase reaction, and can reappear after rechallenge with a different bisphosphonate. Withdrawal of the drug is generally needed for resolution of ocular symptoms, and rechallenge should be avoided.

Skin reactions such as urticaria and pruritus are relatively common, more severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are very rare (<1 in 10,000). Skin rash is a common cause for stopping alendronate.

Hypocalcaemia can follow treatment with bisphosphonates by any route. There is a risk of symptomatic hypocalcaemia in patients with hypoparathyroidism or vitamin D deficiency. Patients receiving bisphosphonates may require calcium and vitamin D supplementation, unless they are receiving the bisphosphonate for hypercalcaemia.

Other adverse effects including hepatotoxicity, nonspecific malaise, anaemia, thrombocytopenia, leucopenia, altered taste, headache and dizziness have been reported with bisphosphonates.

Conclusion:

Though the safety profile of bisphosphonates is good, some adverse effects are not rare and lead to discontinuation of treatment. GI effects are common with oral bisphosphonates. The most prevalent adverse effect of intravenous bisphosphonates is a 'flu-like' acute phase reaction. This is normally self-limiting and may decrease in severity with subsequent infusions. There are growing concerns over two long term safety aspects of bisphosphonate use – osteonecrosis of the jaw and atypical femoral fragility fractures.