

SAFER MEDICATION USE

No. 2

January 2008

BISPHOSPHONATES

for osteoporosis

Gastrointestinal adverse effects are common with all bisphosphonates. With the exception of zoledronic acid, all have been reported to cause oesophageal ulceration, the incidence of which is minimised by adherence to strict administration guidelines. No difference in the risk of serious upper gastrointestinal reactions has been demonstrated between alendronic acid and risedronate. Atrial fibrillation has been associated with zoledronic acid and possibly alendronic acid; further investigation into a link between bisphosphonates and atrial fibrillation is ongoing. Osteonecrosis of the jaw has been reported with bisphosphonates prescribed for osteoporosis, which may be precipitated by dental surgery; the degree of risk in such patients is uncertain and extra vigilance is warranted. All bisphosphonates can cause severe musculoskeletal pain, which generally resolves on discontinuation. A paucity of data in patients with renal dysfunction means all bisphosphonates should be used with caution in severe renal impairment.

Background

Bisphosphonates are used for prophylaxis and treatment of osteoporosis, treatment of Paget's disease and as part of some cancer treatments. The Regional Drug and Therapeutics Centre has previously published information on bisphosphonates.¹⁻³ The National Institute for Health and Clinical Excellence is currently reviewing its guidance on primary and secondary prevention of osteoporotic fractures in post-menopausal women.^{4,5}

Upper gastrointestinal tract adverse effects

All bisphosphonates licensed for the prophylaxis and treatment of osteoporosis, including intravenous preparations, often cause mild gastrointestinal (GI) adverse effects such as dyspepsia, nausea, diarrhoea, and abdominal pain.⁶ No difference in the incidence of such mild upper GI effects has been demonstrated between alendronic acid, ibandronic acid, risedronate or zoledronic acid.⁷

Randomised placebo-controlled trials (RCTs) of all bisphosphonates, except zoledronic acid reported serious upper GI adverse effects, such as oesophageal ulcer, oesophagitis or erosive oesophagitis; however only one trial found a significantly higher risk with etidronate compared to placebo.⁷⁻¹⁰ A recent Cochrane review of alendronic acid for primary and secondary prevention of osteoporotic fractures in post-menopausal women, did not detect a significantly increased risk of developing any upper GI event or oesophageal ulcer

compared with placebo (relative risks 1.03 [95% CI 0.98 to 1.08] and 1.16 [95% CI 0.39 to 3.45] respectively).¹¹ However, RCTs are not necessarily powered to detect these more uncommon serious adverse reactions, which are better detected by spontaneous reporting such as the Yellow Card Scheme. Severe oesophageal effects were reported, post-marketing, with alendronic acid which led to the warning that it should not be prescribed to patients with abnormalities of the oesophagus or factors delaying oesophageal emptying.⁶

PRACTICE POINT— administration guidance for oral bisphosphonates

Patients must be informed of and be able to follow strict administration guidelines with oral bisphosphonates.⁶

- Tablets must be swallowed whole, with a full glass of water on an empty stomach, at least 30-60 minutes before food, whilst standing or sitting upright.
- Patients must not lie down for 30 minutes after administration of alendronic acid and risedronate, or 1 hour after ibandronic acid; and they must not be taken at bedtime or before rising.
- Patients should be advised to stop the bisphosphonate tablets and seek medical attention if they develop signs of oesophageal irritation.

To minimise the risk of upper GI effects, oral bisphosphonates must be administered according to strict guidance and, with the exception of etidronate, use is cautioned in patients with upper GI problems.⁶ A review of RCTs involving either risedronate or alendronic acid in post-menopausal osteoporosis (PMO) suggested that there is little or no increase in risk of upper GI problems provided that bisphosphonates are administered properly.¹²

In women with previous GI disease or concurrent non-steroidal anti-inflammatory drug (NSAID) or aspirin prescription neither alendronic acid, ibandronic acid nor risedronate, were associated with a significant increase in upper GI effects compared to placebo.⁸⁻¹⁰ However, the concurrent prescription of ibandronic acid and NSAIDs is cautioned.⁶

A comparison of weekly alendronic acid 70 mg and risedronate 35 mg over 12 months (n=1,042), demonstrated no statistical difference in the incidence of upper GI adverse effects (22.5% and 20.1% respectively, p=0.364).¹³ Extension of the trial for a further 12 months did not alter the rates of upper GI reactions nor discontinuation rates due to these.¹⁴ A comparison of ibandronic acid 150 mg monthly and alendronic acid 70 mg weekly in PMO (n=1,733) demonstrated a similar incidence of upper GI adverse events (17.5% and 17.2% respectively).¹⁵ Increasing the dosing interval to weekly or monthly does not appear to change the rates of GI adverse events compared to daily dosing for alendronic acid, risedronate or ibandronic acid.¹⁶ A comparison of branded and generic preparations of alendronic acid, over three months, found insufficient evidence to indicate major differences in the incidence of upper GI effects between formulations.¹⁷

Intravenous ibandronic acid when compared to oral administration, was not reported to cause an excess of upper GI reactions.¹⁸ The rates of serious upper GI events were not reported in trials where annual zoledronic acid infusions were compared with placebo or alendronic acid.¹⁹⁻²¹

Atrial fibrillation

An increased incidence of atrial fibrillation (AF), described as serious (i.e. life-threatening or resulting in hospitalisation or disability), was detected in postmenopausal women receiving an annual infusion of zoledronic acid compared to placebo (1.3% vs 0.5% respectively, p<0.001), 94% of cases occurred more than 30 days after infusion.¹⁹ This did not correlate with an increased risk of death due to cardiovascular causes. The hazard ratio associated with zoledronic acid was calculated as 2.35 (95%CI 1.43 to 3.88, p = 0.001).²² A further study comparing zoledronic acid with placebo after surgical repair of hip fracture, did not report a difference in the rate of AF.²⁰

In the Fracture Intervention Trial 1.5% of alendronic acid treated patients developed AF compared with 1.0% of placebo patients, however the difference was not statistically significant (relative risk 1.51, 95% CI 0.97 to 2.40, p=0.07).²³ A retrospective evaluation of six published trials involving risedronate in 15,000

patients, found the incidence of AF, reported as adverse events and serious adverse events, was not significantly different from placebo.²⁴ There are no other published reports of AF with bisphosphonates prescribed for osteoporosis.

As of October 2007 the Medicines and Healthcare products Regulatory Agency (MHRA) had received six reports of suspected AF with bisphosphonates (alendronic acid three, etidronate two, ibandronic acid one).²⁵

PRACTICE POINT – FDA prescribing advice

- The significance of the recent reports of AF with zoledronic acid and alendronic acid is not clear. It is not known whether this is a class effect. An in-depth evaluation of bisphosphonates and AF is ongoing.²⁶
- A change in prescribing practice is not necessary at this time;²⁶ nor is additional patient monitoring required.

Osteonecrosis of the jaw

Most reported cases of osteonecrosis of the jaw (ONJ) have been associated with intravenous bisphosphonates.²⁷ A review of bisphosphonate associated ONJ found most patients (94%) were treated with intravenous bisphosphonates (primarily zoledronic acid and pamidronate) and had multiple myeloma or metastatic breast carcinoma (85%), whilst 4% had osteoporosis treated with alendronic acid (n=13), risedronate (n=1) and alendronic acid in combination with zoledronic acid (n=1); diagnosis was preceded by dental extraction or other dentoalveolar surgery in 60% cases.²⁸ The prevalence of ONJ in oncology patients is 6-10%;²⁸ and is unknown in the general population not exposed to bisphosphonates.

As of October 2007, the MHRA had received 16 spontaneous reports of ONJ with alendronic acid, two with risedronate and one case relating to ibandronic acid prescribed for osteoporosis.²⁵ To date no increased risk of ONJ has been observed with zoledronic acid prescribed for PMO in placebo-controlled trials, however these are of relatively short duration and further information is required to establish the degree of risk in such patients.^{19,20}

PRACTICE POINT – MHRA prescribing advice²⁷

In patients at high risk of ONJ (i.e. cancer, chemotherapy, corticosteroids and poor oral hygiene)

- Consider dental examination before prescribing bisphosphonates.
- Avoid invasive dental procedures during treatment. It is not known if discontinuation of bisphosphonates prior to dental surgery reduces the risk of ONJ.
- If patients develop ONJ, dental surgery may exacerbate the condition.

The incidence of ONJ with lower doses of bisphosphonates used in the longer term for the management of osteoporosis is not known and warrants further investigation. Prescribers are advised to make all patients, especially those at high risk, aware of the potential for ONJ.

Renal impairment

All bisphosphonate drugs undergo renal excretion and accumulation may occur in patients with impaired renal function.⁶ There is limited published data on the effect of impaired renal function on the safety and efficacy of bisphosphonates, due to trial exclusion criteria.

A sub-analysis of the Fracture Intervention Trial showed there was no increase in adverse events following treatment with alendronic acid among women with impaired renal function, 10% of whom had severe renal impairment defined as estimated glomerular filtration rates <45ml/minute.²⁹ A pooled analysis of nine clinical trials of risedronate 5 mg in patients with age related declines in renal function, ranging from mild (creatinine clearance (CrCl) \geq 50 to <80ml/minute) to severe (CrCl < 30ml/minute) impairment, demonstrated a similar incidence of renal function-related adverse events compared to placebo, irrespective of baseline renal function.³⁰ The author suggested treatment with risedronate to be safe in such patients with CrCl of 15-30 ml/minute,³⁰ however this use is outwith the current licence.⁶

PRACTICE POINT

All bisphosphonates should be used with caution in severe renal impairment; however there are variations in the lower limit of CrCl below which a drug is not recommended:⁶

- Alendronic acid <35ml/minute
- Ibandronic acid and risedronate <30ml/minute
- Zoledronic acid <40ml/minute
- Etidronate – caution recommended in all patients with impaired renal function. Treatment in severe renal impairment is contra-indicated.

A comparison of oral and intravenous ibandronic acid in PMO showed renal and urinary adverse reactions to be uncommon and comparable in frequency across all treatment arms (2-3%). No cases of acute renal failure were reported.¹⁸ Zoledronic acid prescribed for PMO has not been shown to impair renal function compared to placebo, when monitored over a three-year

period.¹⁹ However, it has been associated with renal toxicity when used in higher doses for the management of malignancies.¹⁶

Musculoskeletal pain

Severe bone, joint and musculoskeletal pain have been reported with all bisphosphonates, occurring within days, months or years after starting a bisphosphonate.^{6,31} The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.³¹ There may be under reporting of the problem, as pain may be attributed to osteoporosis.³² Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas some have reported slow or incomplete resolution.³¹ Of the patients who developed musculoskeletal symptoms with alendronic acid, 11% redeveloped pain when rechallenged with the same drug or another bisphosphonate.^{6,32}

This severe musculoskeletal pain is in contrast to the acute influenza type reactions, which have been reported with both ibandronic acid and zoledronic acid. These have been discussed in New Drug Evaluations numbers 74² and 86.³

PRACTICE POINT – FDA prescribing advice

Healthcare professionals should consider whether bisphosphonate use might be responsible for severe musculoskeletal pain in patients who present with these symptoms and consider temporary or permanent discontinuation of the drug.³¹

When should adverse reactions be reported to the MHRA?

All serious suspected adverse reactions to any bisphosphonate should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk). This includes serious upper GI reactions, AF, ONJ, severe musculoskeletal pain and renal dysfunction suspected to be related to bisphosphonate use. All adverse reactions to black triangle drugs (which include ibandronic acid and zoledronic acid⁶) should be reported, as should all suspected serious reactions to any drug, herbal or OTC medicine.

The Yellow Card Centre Northern and Yorkshire can provide support and guidance on any adverse reaction related enquiry or completion of a Yellow Card. Information is available via our website [link](#).

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KEY RCT – Randomised Controlled Trial, R – review, G – Guidelines, Abs – Abstract