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Safety Considerations with Bisphosphonates for the Treatment of Osteoporosis

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Contents

Abstract

Bisphosphonates are the most commonly prescribed medications for the treatment of osteoporosis. Although evidence supports a good safety profile for these agents, numerous tolerability issues have been associated with their use. This review provides an overview of the safety issues associated with the nitrogen-containing class of bisphosphonates and discusses the potential effect of these issues on adherence. The review specifically considers upper gastrointestinal (UGI) adverse events (AEs), renal toxicity, influenza-like illness, osteonecrosis of the jaw and evidence on how to treat or prevent these events.

In clinical trials, UGI AEs, including severe events such as oesophageal ulcer, oesophagitis and erosive oesophagitis, have been reported at similar frequencies in placebo- and active-treatment arms. However, postmarketing studies have highlighted UGI AEs as a concern. These studies show that a significant portion of patients are less compliant with administration instructions outside strict clinical trial supervision, and when oral bisphosphonates are not administered as directed, patients are more likely to experience UGI AEs. Some clinical trials with oral bisphosphonates have suggested that a decrease in the frequency of administration may lead to improvement in gastrointestinal tolerability. In the authors' experience, the issue of UGI tolerability can be minimised by explaining to the patient and/or caregiver the importance of following administration instructions.

Intravenous (IV) bisphosphonates have been recently approved for use in osteoporosis, offering an alternative regimen for patients with osteoporosis.

Earlier generation IV bisphosphonates (e.g. etidronate) have been associated with acute renal failure. Alternatively, late-generation IV bisphosphonates (i.e. ibandronate) have shown a better safety profile in relation to renal toxicity.

Influenza-like illness, often referred to as an acute-phase reaction, covers symptoms such as fatigue, fever, chills, myalgia and arthralgia. These symptoms are transitory and self-limiting and usually do not recur after subsequent drug administration. Symptoms of influenza-like illness have been associated with both IV and oral bisphosphonates.

Osteonecrosis of the jaw has also been associated with IV bisphosphonate treatment, particularly in patients treated with high doses. A small number of patients with cancer and osteoporosis using oral bisphosphonates have also reported this AE. As osteonecrosis of the jaw is difficult to treat and is often associated with dental procedures and poor oral hygiene, preventive measures seem to be the best management option for patients taking bisphosphonates.

Overall, the safety and tolerability profile of the nitrogen-containing bisphosphonates is good, and long-term treatment does not appear to carry a risk of serious AEs. By encouraging adherence to administration instructions physicians can minimise certain complications, such as UGI intolerability. By being aware of other potential safety issues, such as renal impairment, influenza-like illness and osteonecrosis of the jaw, physicians can detect these AEs early in the course of treatment.

Nitrogen-containing bisphosphonates such as alendronate, risedronate and ibandronate are highly efficacious and are the current standard treatment for postmenopausal osteoporosis. Bisphosphonate treatment has been reliably associated with clinically significant increases in bone mineral density, suppression of bone-turnover markers and reductions in fracture risk.[1-3] The nitrogen-containing bisphosphonates exert their antiresorptive activity on osteoclasts primarily by inhibiting farnesyl diphosphate synthase, thereby blocking prenylation of guanosine triphosphate-binding proteins and disrupting several cellular processes.[4] Their mechanism of action is distinct from the non-nitrogen-containing bisphosphonates, which will not be considered here.

In Europe, Japan and the US, osteoporosis is estimated to affect 75 million men and women.[5] Postmenopausal osteoporosis affects approximately 55% of women aged >50 years in the US,[6] and is becoming an increasingly important problem with the ageing global population, creating serious cost implications for public health. In the US alone, it is estimated that fracture-related costs will be at least $US23.5 billion by 2025.[7]

Postmenopausal osteoporosis is a chronic condition; therefore, safe, convenient and long-term treatment is required. Oral bisphosphonate administration instructions specify that the drug must be taken on an empty stomach, without concomitant medications, with plain water and that the patient must maintain an upright posture for up to 1 hour following administration. As many as one in four patients are non-compliant with these instructions.[8] When oral bisphosphonates are not administered as directed, patients are more likely to experience uncomfortable upper gastrointestinal (UGI) adverse events (AEs)[9] and this leads to greater potential for discontinuation. Poor adherence to therapy accounts for as much as 16% higher fracture rates and 14% higher hospital costs when compared with outcomes in patients adherent to therapy.[10]

In clinical trials evaluating risedronate and alendronate, there was no evidence of any emergent problems in specific AE classes, and withdrawals due to AEs were similar to placebo for patients

treated with either alendronate[11-13] or risedronate.[14-16] However, a potential concern has been highlighted in postmarketing studies of real-world patients taking medications outside strict clinical trial supervision. In one study, 219 patients attending an osteoporosis clinic were questioned; in total, 38% experienced AEs while receiving risedronate, with UGI events cited as the most common AE.[8] In another study, 19% of patients discontinued alendronate treatment due to AEs.[17] Consequently, limiting the potential for AEs is a good strategy for increasing the adherence, and ultimately the efficacy, of osteoporosis treatment.[18]

Although oral bisphosphonates are effective and safe in treating postmenopausal osteoporosis, the intravenous route of administration may enhance adherence by providing an alternative regime for patients who have difficulties complying with the strict schedule required for oral bisphosphonates or who have issues with reliable self-administration. To that end, bisphosphonates have been developed or are being developed for intermittent intravenous administration: intravenous ibandronate (Boniva® [1] injection) received US FDA approval as a quarterly injection in January 2006 and zoledronic acid is being developed as an annual infusion, following promising clinical trial results.[19] However, there are some concerns regarding intravenous bisphosphonates with respect to influenza-like illness or acute-phase reactions,[19] renal toxicity[20,21] and osteonecrosis of the jaw,[22] which are described in sections 3–5.

The review provides a summary of safety and tolerability issues relating to the use of oral and intravenous nitrogen-containing bisphosphonates in the treatment of patients with postmenopausal osteoporosis.

1. Literature Search Methodology

A literature search was conducted in PubMed in November 2004 with no limit on the publication date. The search was updated throughout the writing process until March 2005. Keywords and phrases included 'nitrogen-containing bisphosphonates', 'alendronate', 'ibandronate', 'risedronate', 'zoledronic acid', 'osteoporosis', 'adverse events', 'gastrointestinal intolerance', 'osteonecrosis of the jaw', 'renal toxicity', 'influenza-like illness', 'side effects' and 'safety' in various combinations. Only articles written in the English language were included. Additional articles were found in the citations from articles identified in the PubMed search. A number of websites, both commercial and public, were also accessed and cited, and data from published abstracts were included.

2. Upper Gastrointestinal Tolerability

Alendronate, which has been available in oral form by prescription since September 1995, has the greatest amount of efficacy and safety data. A detailed analysis of postmarketing data for daily alendronate from September 1995 to March 1996 found a number of cases of oesophageal AEs with the drug.[23] At that time, approximately 475 000 patients had received prescriptions; of 1213 reported AEs, 199 patients had an oesophageal AE, including 51 with a serious or severe event such as oesophageal ulcer, oesophagitis or erosive oesophagitis. Endoscopic examination of 36 patients found that oesophagitis was consistent with a chemical cause, and cessation of alendronate therapy, combined with treatment for the oesophageal irritation, was associated with recovery in most cases. The majority (17 of 28 [61%]) of patients with reported oesophageal complications for whom administration information was available appear to have been noncompliant with product instructions with respect to the quantity of water taken with the tablet or remaining upright. On the basis of this postmarketing survey, the administration instructions were amended to stipulate that the drug should be taken when the patient is arising for the day, an instruction that was applied to subsequent oral bisphosphonates, including risedronate and ibandronate.

If not taken properly (without water or while laying down), the tablet may remain in contact with

1 The use of trade names is for product identification purposes only and does not imply endorsement.

the oesophageal mucosa for a long time, as it occurs in cases of reduced oesophageal motility, potentially resulting in oesophageal irritation. Clinically relevant concentrations of alendronate and risedronate were found to suppress the growth of normal human epidermal keratinocytes, via inhibition of farnesyl diphosphate synthase, the same enzyme affected in osteoclasts.[24] Therefore, bisphosphonates are contraindicated in patients with oesophageal abnormalities that delay oesophageal emptying (e.g. stricture or achalasia) or impaired motility. Nonetheless, there have been some reports of severe oesophageal reactions to alendronate, even in patients who had apparently complied with strict administration regimens.[25] Continued postmarketing surveillance is therefore required to identify individuals that may be at risk of these rare but severe AEs.

Although the incidence of UGI AEs is reportedly high during bisphosphonate therapy, an important consideration to keep in mind is that the prevalence of overall UGI complaints amongst older women is high.[26] The large-scale Fracture Intervention Trial of alendronate randomised women to placebo or alendronate 5 mg/day, with the alendronate dose increasing to 10 mg/day after 2 years.[27] The overall incidence of UGI AEs was 46.2% and 47.5% for placebo and alendronate, respectively, and the incidence of oesophageal events was 9.4% and 10% for placebo and alendronate, respectively. Even among patients at higher risk for UGI AEs, such as those aged ≥75 years with a history of UGI disease or those using NSAIDs, alendronate therapy was not associated with significantly increased UGI events compared with placebo. In addition, because it is important for patients to have prior knowledge of possible adverse effects of their medication, they may be more sensitised to UGI events, which might also encourage exaggerated incidences.

Taggart et al.[28] analysed UGI safety data from nine randomised, placebo-controlled trials of daily risedronate for the treatment of osteoporosis (postmenopausal and glucocorticoid-induced in men and women) in approximately 10 000 patients. Owing to the association of UGI AEs with some bisphosphonates, the risedronate trials paid particular attention to such events and included endoscopic analyses where appropriate. Even though 61% of patients had a history of gastrointestinal (GI) tract disease and 38.7% had active GI tract disease at baseline, the proportion of patients experiencing UGI AEs was virtually identical at 29.6% and 29.8% for placebo- and risedronate-treated groups, respectively. The use of NSAIDs was not associated with an increased incidence of UGI events relative to the placebo-treated groups. In these nine clinical trials, endoscopy was performed in 349 patients, 167 receiving placebo and 182 receiving risedronate. Most of these patients had a history of GI disease and/or NSAID use, and there were no significant differences between placebo and risedronate groups in terms of inflammation, erosion or ulceration of the oesophagus, stomach or duodenum.[28]

In two studies on patients receiving short-term treatment with alendronate or risedronate, endoscopic analyses revealed low levels of UGI erosions and ulcers.[29,30] One of these studies[29] used both placebo and placebo with aspirin (acetylsalicylic acid) as comparators, and standardised oesophageal scores were found to be comparable for all groups. However, alendronate and risedronate were associated with significantly lower mean gastric and duodenal erosion scores compared with aspirin ($p < 0.001$).[29] The second study,[30] which was not placebo controlled, reported a significantly lower incidence of UGI erosion with daily alendronate than with daily risedronate, although mean oesophageal and duodenal endoscopy scores were similar.

Evidence supporting the good GI tolerability profile of bisphosphonates comes from FACT (Fosamax Actonel Comparison Trial), which compared once-weekly alendronate with once-weekly risedronate. In this study, 41% of patients received concomitant NSAIDs and 25% had a prior history of UGI disorders.[31] Both treatments were well tolerated, with no significant differences in UGI AEs (22.5% for alendronate and 20.1% for risedronate) or number of discontinuations related to these AEs (2.5% for alendronate and 3.0% for risedronate). However, another study reported that the relative risk of patients developing a UGI disorder with

alendronate and concommitant NSAIDs was 1.7 times (95% CI 1.1, 2.6) that of alendronate alone.[32] In fact, there is some evidence that alendronate and naproxen, when taken together, have a synergistic ulcerogenic effect.[33] Such an effect is potentially problematic, since the concomitant use of these two drugs is common in the elderly, as observed in patients included in clinical trials of osteoporosis.[31,32,34]

Two studies have compared the safety of ibandronate with placebo in women with postmenopausal osteoporosis. The phase I monthly oral pilot study evaluated placebo versus various monthly ibandronate doses in 144 women.[35] The overall AE profile was similar for the placebo and treatment arms; however, UGI AEs occurred in 12 (33%), 3 (17%), 11 (61%), 15 (42%) and 15 (42%) patients in the placebo, 50mg, 50/100mg, 100mg and 150mg treatment groups, respectively. A second placebo-controlled ibandronate trial was the BONE (Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe) study, which examined daily (2.5mg) and intermittent (20mg every other day for 12 doses every 3 months) ibandronate administration regimens.[34] Despite approximately 30% of patients having a history of GI disorders, UGI AEs occurred in 31.1%, 31% and 30.4% of the 975, 977 and 977 patients taking placebo, daily and intermittent ibandronate, respectively. The most frequently occurring of these events were dyspepsia, nausea, gastroenteritis, vomiting and GI pain. Oesophagitis occurred in 1%, 1.5% and 1% of patients in the placebo, daily and intermittent groups, respectively. There was no association between the use of aspirin or NSAIDs and the incidence of UGI complications in BONE. The lower incidence of UGI events found with ibandronate and risedronate relative to alendronate may be due to differences in the baseline characteristics of the patients since, within trials, placebo- and bisphosphonate-treated patients had similar rates of UGI AEs.

In an attempt to improve persistence with bisphosphonate treatment, administration intervals have been extended from daily to weekly to monthly. Results from a trial comparing oral alendronate 10 mg/day, 35mg twice weekly and 70mg once weekly found fewer serious UGI AEs and fewer oesophageal events in the weekly arm; however, this difference was not statistically significant.[13] A 2-year study comparing once-daily and once-weekly risedronate found no statistically significant differences in the incidence of UGI AEs.[36] The MOBILE (Monthly Oral Ibandronate In Ladies) study compared the efficacy and safety of ibandronate 2.5 mg/day with three different monthly oral doses in postmenopausal women. Over 2 years, UGI AEs occurred in 22.8%, 19.9%, 25.8% and 22.5% of patients in the daily, 50mg/50mg (on consecutive days), 100mg and 150mg monthly ibandronate doses.[37]

To summarise, the rates of UGI AEs in clinical trials are generally similar for the placebo- and active-treatment arms. There is evidence for UGI intolerability with individual bisphosphonates, along with a potential mechanism that may account for such events. In our experience, the issue of UGI tolerability can be minimised by explaining to the patient and/or caregiver the importance of adhering to administration instructions.

3. Renal Toxicity

Intravenous bisphosphonates are the current standard of care for the treatment of hypercalcaemia of malignancy and for the prevention of bone metastasis in patients with advanced cancers and at high risk for bone metastasis.[38] In such patients, earlier generation bisphosphonates (e.g. etidronate and clodronate)[20] that require administration at higher doses, and a late-generation bisphosphonate, zoledronic acid,[21] have been associated with acute renal failure. Two long-term trials of zoledronic acid in patients with cancer reported renal toxicity with an infusion of zoledronic acid 8mg every 3 weeks; owing to these safety concerns, patients who were receiving this dose were subsequently transitioned to a 4mg dose, which was found to have better renal safety.[39,40] In a trial involving postmenopausal women with low bone mineral density, zoledronic acid infused quarterly (0.25mg, 0.5mg and 1mg), biannu-

ally (2mg) and annually (4mg) did not appear to impair renal function.[19]

Intravenous ibandronate administered as a 2mg bolus injection or as a 6mg infusion over 1 hour has shown no evidence of renal toxicity and has a safety profile similar to placebo in patients with metastatic bone disease.[41] In another study of 312 patients with metastatic bone disease, there was a low incidence of clinically significant renal AEs with intravenous ibandronate and placebo (4% and 4.5%, respectively) and none of these were regarded as serious or prompted withdrawal from treatment.[42] Furthermore, when intravenous ibandronate was infused over 15 minutes, one relatively high dose (6mg) in 20 patients with metastatic bone disease showed no renal impairment during the 3 days after administration.[43] Since this 6mg dose is twice that approved by the US FDA for quarterly ibandronate injections for postmenopausal osteoporosis, it is likely that renal toxicity will be less of an issue when treating postmenopausal osteoporosis. To date, no cases of renal toxicity have been attributed to ibandronate,[34,44] and renal safety is strictly monitored in clinical trials. Indeed, safety results from the DIVA (Dosing Intravenous Administration) study comparing oral ibandronate 2.5 mg/day with intravenous ibandronate bimonthly (2mg) and quarterly (3mg) found the overall incidence of renal and urinary AEs was low and comparable across the three treatment arms (3.9%, 4.5% and 3.2%, for the daily, bimonthly and quarterly doses, respectively).[45]

4. Influenza-Like Illness

The term 'influenza-like illness' covers symptoms such as fatigue, fever, chills, myalgia and arthralgia, and is often referred to as an 'acute-phase reaction'. Symptoms of influenza-like illness are normally associated with intravenously administered bisphosphonates,[19,46] but also occur with oral bisphosphonates.[37,47,48] These symptoms are transitory and self-limiting, usually lasting 1–3 days.[49] Normally, symptoms do not recur after subsequent drug administration. The mechanism of acute-phase reactions associated with nitrogen-containing bisphosphonates seems to be related to the inhibition of the mevalonate pathway, whereby the bisphosphonate induces rapid and copious production of the proinflammatory cytokines tumour necrosis factor-α and interleukin-6 by $\gamma\delta$T cells.[50,51] Prior administration of an HMG-CoA reductase inhibitor (statin) was found to prevent the overproduction of these cytokines and could help alleviate influenza-like illness/acute-phase reactions in patients receiving nitrogen-containing bisphosphonates.[50,51]

5. Osteonecrosis of the Jaw

The pathology of osteonecrosis (or avascular necrosis) is poorly understood, but it is characterised by death of bone, resulting in the collapse of architectural bony structure, loss of function and bone pain.[52] The most common cause of osteonecrosis is trauma, but it is also associated with corticosteroid usage, radiotherapy, chemotherapy, systemic lupus erythematosus and alcoholism. Osteonecrosis is responsible for at least 10% of the 500 000 total joint replacements performed every year in the US, and primarily affects men and those aged 30–60 years.[52]

Cases of a syndrome called osteonecrosis of the jaw were first reported in patients receiving chemotherapy and intravenous pamidronate or zoledronic acid alone or sequentially.[22] However, these clinical events are substantially different from avascular necrosis of the hip, as they usually present as open lesions of the oral mucosa with bone exposure and frequent infections. Although most of these cases occurred in patients who had been treated with heavy doses of intravenous bisphosphonates, a small number of patients with cancer and osteoporosis using the oral bisphosphonates alendronate and risedronate experienced problems of a similar nature, as reviewed by Migliorati et al.[53] In an Office of Drug Safety postmarketing safety review,[54] osteonecrosis of the jaw was reported in 12 patients who were taking oral alendronate and in one patient who was taking oral risedronate. In 2005, the US FDA added a precaution to the labels of all bisphosphonates, part of which is reproduced here: "Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an

oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment". As osteonecrosis of the jaw in patients receiving bisphosphonates is difficult to treat and is often associated with dental procedures and poor oral hygiene, preventive measures seem to be the best management option according to an American Academy of Oral Medicine position paper.[53]

6. Long-Term Safety and Mortality

The long-term safety of nitrogen-containing bisphosphonates in patients with postmenopausal osteoporosis appears to be good, based on over a decade of experience with alendronate.[18,55] The mechanism of action of bisphosphonates dictates that the drug must be present at active bone remodelling sites in sufficient concentrations and, in order to gain maximum efficacy, the drug must be given repeatedly.[56] This is because the bisphosphonate molecules are bound to the bone surface and are then covered with a mineralised matrix by osteoblasts, the drug effectively becoming inert and inaccessible.[56] However, the long-term safety profile of zoledronic acid may be different from other bisphosphonates, since the mechanism of its extended suppression of bone remodelling remains to be elucidated.[19,56]

Concerns have been raised regarding excessive suppression of bone turnover, and it is postulated that this may lead to increased susceptibility to, and delayed healing of, non-vertebral fractures. Evidence for this concept was given in a case report of nine men and women who had been receiving alendronate for between 3 and 8 years and who had spontaneous non-vertebral fractures;[57] however, in two of these patients, corticosteroid use complicated the clinical picture. Histomorphometric examination of bone biopsies showed evidence of severe suppression of bone turnover. Although the duration of follow-up was not specified, no new fractures were reported following cessation of alendronate. Even though severe suppression of bone turnover appears to be rare, physicians should be aware of this potential AE, especially in the presence of co-morbid conditions and/or concomitant medications such as corticosteroids.

Finally, a retrospective study of approximately 8000 patients in three risedronate clinical trials found no overall difference in mortality with risedronate treatment compared with placebo for all cardiovascular or other causes and all cancers.[58] There were more deaths due to lung cancer in patients taking risedronate 2.5mg versus placebo or risedronate 5mg, but this was attributed to chance or a follow-up bias owing to the fact that patients taking the 5mg dose had no increase in lung cancer rates.

7. Conclusion

As documented recently in the report by the US Surgeon General on osteoporosis, in order to improve adherence to therapy there is a need to simplify and organise treatment regimes and address patients' concerns about adverse effects.[18] Overall, the safety and tolerability profile of the bisphosphonates is good, and long-term treatment does not appear to carry a risk of serious AEs or death. A commonly perceived AE of interest to patients and physicians is UGI intolerability, but strict adherence to administration instructions can minimise such complications. Addressing UGI AEs with patients not only enhances the physician-patient relationship, but may also improve adherence directly through reducing the incidence of AEs.

The choice of administration regimens now available for treating postmenopausal osteoporosis – daily and weekly oral alendronate and risedronate, monthly oral ibandronate and quarterly intravenous ibandronate – should help improve clinical outcomes by offering individualised solutions and incorporating patient preference into administration decisions. With intravenous bisphosphonates in particular, physicians and other healthcare professionals should be alert to other infrequent adverse effects, such as influenza-like illness/acute-phase re-

actions, renal impairment and osteonecrosis of the jaw.

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