Management of the adverse effects associated with intravenous bisphosphonates

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Intravenous bisphosphonates are widely used to treat hypercalcemia and to reduce skeletal-related morbidity among cancer patients. However, serious complications, generally occurring in less than 2% of patients participated in phase III clinical trials, including acute systemic inflammatory reaction, ocular inflammation, renal failure, nephrotic syndrome, electrolyte imbalance, and osteonecrosis of the maxilla and mandible have all been increasingly reported. Yet, strategies to deal with these complications are becoming clear. Acute systemic inflammatory reaction is often self-limited and becomes less intense during subsequent treatments. For patients who develop ocular symptoms, prompt ophthalmologic evaluation is crucial to determine the safety of a subsequent bisphosphonate therapy. Patients who receive long-term pamidronate should be evaluated at intervals for early sign of nephritic syndrome as timely cessation of the agent may result in a full recovery. To reduce the risk of severe electrolyte abnormalities, particularly hypocalcemia, correcting any pre-treatment electrolyte abnormality and supplementing vitamin D and calcium may be helpful. Finally, to reduce the risk of osteonecrosis of the maxilla and mandible, obtaining a full dental evaluation before treatment and avoidance of invasive dental procedures is suggested. The three commonly used intravenous bisphosphonates (pamidronate, zoledronic acid, and ibandronate), are generally safe; ibandronate has to date been the least reported to be associated with renal side effects. As clinical indications of intravenous bisphosphonates continue to expand, prescribing clinicians should be familiar with these possible adverse effects and discuss them with patients before commencing or continuing on therapy.

Key words: bisphosphonate, pamidronate, zoledronic acid, clodronate, ibandronate, side effect

introduction

Bisphosphonates are synthetic analogues of pyrophosphate, a natural regulator of bone metabolism found abundantly in bone matrix [1]. These compounds inhibit the differentiation of osteoclastic precursors, induce apoptosis of osteoclasts, and stimulate the release of osteoclastic inhibitory factor from osteoblasts [2]. In addition, bisphosphonates that closely resemble pyrophosphate such as clodronate, etidronate, and tiludronate are incorporated into non-hydrolyzable ATP analogues, interfering with cellular metabolism [2]. Newer nitrogen-containing bisphophonates such as pamidronate, alendronate, risedronate, zoledronate, and ibandronate also inhibit the mevalonate pathway of cholesterol synthesis and prevent post-translational prenylation of small guanosine triphosphate–binding proteins in osteoclasts [3].

Pamidronate, ibandronate, and zoledronic acid are the most potent and widely-used intravenous bisphosphonates. Intravenous clodronate and etidronate are less potent, with less affinity to bone, requiring prolonged infusion time and thus becoming less popular [4]. Zoledronic acid is the most potent: about 850 times more potent than pamidronate [5]. With a high affinity to bone, zoledronic acid concentration in bone is greater than 100 fold of plasma and will decline only slightly after 6 months [6]. Currently, the Food and Drug Administration of the United States (FDA) has approved pamidronate for treatment of hypercalcemia of malignancy, Paget’s disease, osteolytic bone metastases of breast cancer, and osteolytic lesions of multiple myeloma [7, 8]. Zoledronic acid is approved for hypercalcemia of malignancy and bone metastases from solid tumors including hormone-independent prostate cancer. Intravenous ibandronate and clodronate are currently approved in the European Union. The current recommended dosage of pamidronate for hypercalcemia of malignancy is as a 60–90 mg infusion over 2–24 h; for osteolytic lesions in myeloma, 90 mg over 4 h; and in breast cancer, 90 mg over 2 h. Zoledronic acid, however, is administered as a 4-mg infusion not less than 15 min for all patients with bone metastasis who have normal renal function. The maximal recommended dose...
for hypercalcemia is 4 mg. For ibandronate, the usual administration is 6 mg infusion over 1 to 2 h. The typical dosing interval is every 3 to 4 weeks, but a repeat dose can be given sooner to treat hypercalcemia. Although the optimal duration of bisphosphonate therapy has never been subjected to clinical trials, treatment for cancer with bone metastasis and myeloma with osteolytic lesion is generally recommended until patients cannot tolerate treatment or experience a substantial functional decline [9, 10].

To date, there have been reports of multiple serious adverse effects associated with all drugs. Some have resulted from off-label uses, but others were seen at the recommended dosage and infusion time. Since the clinical indications of these agents continue to expand, it is important for clinicians to prevent, recognize, and manage these possible complications effectively and expeditiously.

article search

Medline database from 1965 to October 2005 was searched through PubMed using keywords, pamidronate, ibandronate, clodronate, and zoledronic acid in combination with side effects including adverse reaction, fever, ocular complication, renal failure, glomerulonephritis, hypocalcemia, hypophosphatemia, hypomagnesemia, and osteonecrosis. References of the retrieved articles were checked for additional articles. Prescribing information and published abstracts from annual meetings at the European Society for Medical Oncology, American Society of Clinical Oncology, and American Society of Hematology were also included. Since the objective of this review is to comprehensively include possible side effects of pamidronate and zoledronic acid, selected entries were included regardless of evidences of an established causal relationship.

acute systemic inflammatory reactions

In addition to an occasional inflammatory reaction seen at the infusion site, acute systemic inflammatory reactions, characterized by fever, myalgia, arthralgia, nausea, vomiting, and edema are commonly observed after intravenous administration of bisphosphonates. For instance, fever has been reported in 15–30% of patients receiving pamidronate, varied by the patient’s underlying diseases [11, 12]. With regards to zoledronic acid, its use among men with hormone-refractory prostate cancer and bone metastasis is associated with fever in 21% and myalgia in 25%, compared with 13% and 18% among the placebo-treated patients [12]. Zoledronic acid use among women with breast cancer and bone metastasis is associated with fever in 55% of patients, compared with 33% in the placebo arm [13]. In a phase III study of patients with breast cancer or myeloma, the incidences of fever and myalgia from zoledronic acid were equivalent to those from pamidronate—over 30% of patients [14, 15]. Intravenous ibandronate appears to be less associated with such flu-like symptoms, when directly compared with pamidronate [16].

Typically occurring within 48 h of infusion, fever is usually low-grade, though occasionally associated with rigors [17–19]. Accompanying bone pain has also been reported in over half of the patients [14, 15]. The pain, however, may occur without fever and usually starts about 12 h after infusion, commonly felt in spines, ribs, and lower limbs, not necessarily near the site of metastases. Severe pain limiting daily activity and lasting several days has been described uniquely among patients with cystic fibrosis receiving pamidronate [20]. For the elderly, these musculoskeletal symptoms may cause an unsteady gait; therefore, fall precautions should be exercised [21]. Other manifestations that may be related to acute systemic inflammatory reactions are respiratory symptoms and serositis. Acute dypnea and pneumonitis have been reported with pamidronate in children with osteogenesis imperfecta who have underlying pulmonary disease [22, 23]. These respiratory symptoms are rare. In a phase III study, of 182 patients with breast cancer randomized to receive pamidronate, one patient developed acute dypnea (0.5%), and subsequent clinical trials of pamidronate and zoledronic acid found no increased incidence of dyspnea [7, 8, 24]. Of 308 patients treated with intravenous ibandronate in a phase III trial, one patient developed pulmonary edema [25]. Aseptic peritonitis following the initial acute phase reactions resulting in unnecessary laparotomy has been reported in one patient 12 days after pamidronate infusion [26].

Laboratory abnormalities during the acute systemic inflammatory reactions include increased C-reactive protein, mild anemia, and leucopenia; however, ibandronate infusion may be associated with transient lymphocytosis [27]. C-reactive protein is increased in the majority of patients following pamidronate infusion. Leukopenia is not uncommon with pamidronate. Among patients with osteolytic metastases from breast cancer, it occurred in 9% of patients receiving pamidronate compared with 4% in those receiving placebo [24]. Transient leucopenia, specifically T-helper lymphopenia may be detected within 24 h and a reduction of up to 50% of CD4 positive lymphocytes in peripheral blood has been observed at 3 days [28]. These inflammatory reactions appear to be the result of an increase in cytokine release from macrophages and monocytes.

The reactions typically are self-limited and resolve completely within 24 to 48 h. Supportive and symptomatic management with NSAIDs and acetaminophen is sufficient, although other serious causes of fever such as infection should first be excluded. For patients with baseline anemia or cytopenias, it is recommended that these be monitored after treatment [7, 8]. Most patients will find that bone pain, vomiting, and fatigue lessen during subsequent infusions [17]. Dose reduction for the first treatment or a test dose does not appear to help reduce the incidence or severity of reactions during the treatment, but pre-medication with acetaminophen or ibuprofen may help [15]. In a single case of pamidronate overdosage, the patient experienced hyperpyrexia (39.5°C) and shock; however, these were controlled with steroids [7].

ocular complications

To date, several reports have linked intravenous pamidronate to ocular complications, but there is only one report each from zoledronic acid and clodronate [29, 30]. This complication is uncommon with an estimated incidence of around 0.05% [31].
In the order of frequency, conjunctivitis, uveitis, scleritis, episcleritis, eyelid edema, optic, orbital inflammation, and cranial nerve palsy have been reported [31]. In a randomized trial of pamidronate for women with osteolytic lesion from breast cancer undergoing hormone therapy, one of the 182 patients (0.5%) randomized to receive pamidronate developed an ‘allergic reaction’ in her left eye [23]. Predisposing factors for this complication remain unknown and most affected patients have no underlying ophthalmologic disease. It is seen in both patients with underlying benign and malignant diseases [32, 33]. Conjunctivitis, uveitis, scleritis, and orbital inflammation have an established causal relationship with pamidronate based on dechallenge and rechallenge experiments. Some authors have described xanthopsia and retrobulbar neuritis, but the causal relationship is unclear [34, 35].

Occurring within 6 to 48 h after infusion, these symptoms are most frequently reported after the first or second infusion, although they may manifest as late as after the 6th infusion [36]. Most patients had antecedent acute phase reactions with fever or flu-like symptoms [36, 37]. Red eyes, photophobia, blurred vision, orbital pain, epiphora, and diplopia usually in both eyes may be present. Examination may reveal hypopyon, chemosis or proptosis, indicating uveitis.

Uveitis and scleritis may be anterior, posterior, or both [36]. In severe cases, there may be periorbital edema and erythema mimicking orbital cellulitis (Figure 1) [38, 39]. Cranial nerve III and IV palsy due to swollen rectus muscle may occur and visual acuity can greatly and rapidly deteriorated [40]. Computerized tomography of the eye can confirm rectus muscle edema [38].

Based on the observation that fever and flu-like symptoms often herald this complication, many have suggested that ocular complication is a spectrum of the acute phase reactions [41]. Pamidronate and zoledronic acid share several homologies with non-peptide (gamma, delta) T-cell ligands that activate antigenic receptor and induce cytokine release, leading to inflammation [42].

Whether further treatment with pamidronate or zoledronic acid can be safely continued or not will depend on a precise diagnosis of this complication. Therefore, a formal ophthalmologic evaluation is crucial. Patients with isolated conjunctivitis or episcleritis have a good prognosis—often experiencing a complete resolution of symptoms without specific treatment after a few days and re-treatment with bisphosphonates is generally safe [31, 36]. For these patients, non-steroidal anti-inflammatory eye drops can mitigate the symptoms. Patients with episcleritis, in particular, often respond well to topical inflammatory eye drops [43]. On the other hand, those with uveitis, scleritis, or global orbital inflammation may develop serious consequences—sometimes requiring hospitalization for close observation. Most reports have used systemic steroids, steroid eyedrops, and cycloplegics and one report describes a patient who underwent a forced dilation with topical atropine and intracorneal injection of adrenaline because of the development of adhesions [38–41, 44]. Complete recovery, though possible, often takes several weeks to achieve and in many cases, residual visual impairment persists. Further treatment with the offending bisphosphonate is thus not recommended for patients with uveitis, scleritis, or panendopthalmitis [31, 39]. Some patients do well with switching to etidronate, a non-nitrogen containing bisphosphonate [44]. Ocular complications have also been reported among patients receiving alendronate or risedronate—the bisphosphonates similarly containing nitrogen—and cross-reaction in a patient who switched from risedronate to pamidronate has been observed [45–47].

**Figure 1.** Acute uveitis 48 h after zoledronic acid infusion causing pain and blurring of vision. Examination shows chemosis and posterior synchiae. (Reproduced with permission from Macmillan Publisher Ltd, Eye 2005; 19(2). Copyright 2005).

**Acute and chronic renal failure**

Zoledronic acid and pamidronate have been associated with both acute and chronic renal failure (Table 1) [48–62]. To date, there have been more reports of renal failure associated with zoledronic acid than with pamidronate. Ibandronate infusion appears to have the least documented nephrotoxicity, with the incidence of renal impairment comparable to placebo [25, 63]. Although acute renal failure may be clinically reversible, varying degrees of irreversible impairment may persist and eventually lead to chronic renal failure. In addition, pamidronate has been associated with nephrotic syndrome, tubulointerstitial nephritis, and Fanconi syndrome (aminoaciduria, glycosuria, low serum uric acid).

The risk of renal failure is directly related to the drug infusion time and dosage [7, 8]. High-dose zoledronic acid with short infusion time is strongly nephrotoxic [64–67]. Using the recommended infusion time and dosage, the incidence of renal impairment (an increase in serum creatinine of 20.5, if baseline level <1.4 or ≥1, if baseline ≥1.4) is 9–10% of patients with multiple myeloma or breast cancer receiving zoledronic acid or pamidronate [14]. It is important to note that renal impairment can be seen among placebo-treated patients as well. Outside of clinical trials, the incidence of renal failure associated with zoledronic acid varies by the patients’ underlying diseases from 10–20% [68–70]. Previous treatments with bisphosphonates, advanced age, and multiple cycles of therapies increases the risk, although safe treatment beyond 10 years has been reported [59, 68, 69, 71]. Patients with baseline renal impairment, who often have functional hypertrophy of the remaining nephrons are also at increased risk [72].
The onset of renal dysfunction varies (Table 1). In the largest report of zoledronic acid-associated renal failure containing 72 patients, the complication was diagnosed at a median of 2 months after the first infusion [59]. Eighteen patients (25%) developed renal failure after a single infusion and of these, renal failure was found at a median of 10 days after the infusion. Long-term follow-up indicates that 38% of patients required dialysis; the rest often sustained a permanent renal damage with serum creatinine not returning to baseline level. However, patients, especially those with a mild degree of renal impairment, may expect a full recovery. A return of serum creatinine to baseline has been described as early as a few days to up to four months after discontinuation of the drug [60, 61]. As for pamidronate, most reports described renal failure in the setting of heavy proteinuria, but acute renal failure without heavy proteinuria occurring as soon as within 1 week after administration has also been described [48, 53]. Patients who have renal failure in the setting of nephrotic syndrome seem to carry the worst prognosis—there has been no report of a significant recovery of renal function in such patients to date.

Pathological description of the kidney from patients with zoledronic acid-associated renal failure is typically characteristic of acute tubular necrosis [60]. Electron microscopic study will demonstrate a loss of brush border of the tubular cells and many authors have suggested that the pathogenesis is similar to the effect of these agents observed in osteoclasts: the loss of brush border is analogous to the loss of ruffled border in osteoclasts [60]. Bisphosphonates can interfere with the ATP-dependent metabolic pathway and damage the cytoskeletal structure of tubular cells.

In addition to discontinuing the bisphosphonate, available treatment for renal failure has only been largely supportive. Therefore, prevention is crucial. This includes adequate hydration, checking serum creatinine before each infusion, avoiding concurrent nephrotoxic agents, reducing the dosage for patients with mild renal insufficiency (for zoledronic acid), and withholding treatment in the presence of renal deterioration [7, 8]. In general, treatment is not recommended if serum creatinine is greater than 3 mg/dl or creatinine clearance less than 30 ml/min (with a possible exception in hypercalcemia of malignancy). Pamidronate and zoledronic acid should be withheld, if serum creatinine increases greater than twice of baseline or greater than 0.5 mg/dl for patients with baseline ≤1.4 mg/dl and >1 mg/dl for others [73]. Limited safety data is available among patients with serum creatinine greater than 2 mg/dl. Pamidronate can be used safely for short-term treatment of hypercalcemia among patients already undergoing dialysis [74]. When treatment with zoledronic acid is necessary for patients with creatinine clearance between 30–60 ml/min, the manufacturer has recommended a dose reduction to 3, 3.3, and 3.5 mg for baseline creatinine clearance (calculated by Crockcroft-Gault formula) of 30–39, 40–49, and 50–60 respectively, although the safety data of this approach remains limited [8]. For pamidronate, however, the American Society of Clinical Oncology guideline in 2003 found no evidence to recommend any changes in dosage, infusion time, or interval of therapy among patients with renal impairment but a serum creatinine less than 3 mg/dl [10]. Resumption of treatment after renal deterioration is possible, with careful consideration of risks and benefits. Zoledronic acid has been safely resumed when serum creatinine returns within 10% of baseline, but it should be stopped permanently if no improvement is seen after 4–8 weeks [73]. Finally, some patients with hypercalcemia of malignancy, who often have concurrent renal impairment, have

### Table 1. Publications specifically reporting on renal complications associated with intravenous pamidronate or zoledronic acid

<table>
<thead>
<tr>
<th>Authors, years of publication, [Reference number]</th>
<th>Diagnosis (n)</th>
<th>Treatment with high dosage* (n)</th>
<th>Time from drug initiation to diagnosis of complication</th>
<th>Number of patients with renal impairment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td></td>
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<td></td>
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<tr>
<td>Markowitz et al. 2000 [48]</td>
<td>7 Myeloma (5); Breast cancer (1)</td>
<td>Yes (5)</td>
<td>15–48 months</td>
<td>6</td>
</tr>
<tr>
<td>Van Doorn et al. 2001 [49]</td>
<td>1 Breast cancer</td>
<td>No</td>
<td>11 months</td>
<td>1</td>
</tr>
<tr>
<td>Desikan et al. 2002 [50]</td>
<td>5 Myeloma (5)</td>
<td>Yes (5)</td>
<td>11–48 months</td>
<td>2</td>
</tr>
<tr>
<td>Lockridge et al. 2002 [51]</td>
<td>1 Langerhan’s histiocytosis</td>
<td>No</td>
<td>11 months</td>
<td>1</td>
</tr>
<tr>
<td>Markowitz et al. 2002 [52]</td>
<td>1 Myeloma</td>
<td>Yes</td>
<td>19 months</td>
<td>1</td>
</tr>
<tr>
<td>Banerjee et al. 2003 [53]</td>
<td>1 Hypercalcemia</td>
<td>Yes</td>
<td>1 week</td>
<td>1</td>
</tr>
<tr>
<td>Buysschaert et al. 2003 [54]</td>
<td>1 Hyperparathyroidism</td>
<td>Yes</td>
<td>10 months</td>
<td>1</td>
</tr>
<tr>
<td>Barri et al. 2004 [55]</td>
<td>5 Myeloma (4); Breast cancer (1)</td>
<td>Yes (2)</td>
<td>4–41 months</td>
<td>3</td>
</tr>
<tr>
<td>Smetana et al. 2004 [56]</td>
<td>1 MGUS</td>
<td>No</td>
<td>20 months</td>
<td>1</td>
</tr>
<tr>
<td>Kunin et al. 2004 [57]</td>
<td>1 Myeloma</td>
<td>No</td>
<td>40 months</td>
<td>1</td>
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<tr>
<td>Zoledronic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al. 2002 [58]</td>
<td>3 Myeloma</td>
<td>No</td>
<td>3 months</td>
<td>3</td>
</tr>
<tr>
<td>Chang et al. 2003 [59]</td>
<td>72 Myeloma (42), solid tumors (22), others (8)</td>
<td>Not reported</td>
<td>1–242 days</td>
<td>72</td>
</tr>
<tr>
<td>Markowitz et al. 2003 [60]</td>
<td>6 Myeloma (5), Paget’s disease (1)</td>
<td>No</td>
<td>3–9 months</td>
<td>6</td>
</tr>
<tr>
<td>Tanvetyanon, Choudhury 2004 [61]</td>
<td>1 Carcinoid tumor</td>
<td>No</td>
<td>2 months</td>
<td>1</td>
</tr>
<tr>
<td>Munier et al. 2005 [62]</td>
<td>7 Myeloma (2), solid tumors (5)</td>
<td>No</td>
<td>1–120 days</td>
<td>7</td>
</tr>
</tbody>
</table>

*Treated with pamidronate >90 mg or zoledronic acid >4 mg/3–4wks.
†Renal impairment defined as an increase in serum creatinine of at least 0.5 mg/dl (if baseline level <1.4 mg/dl) or an increase of at least 1 mg/dl (if baseline ≥1.4 mg/dl).

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been treated safely in clinical trials even when the serum creatinine was as high as 4.5 mg/dl [8].

**nephrotic syndrome**

Currently, only intravenous pamidronate has been associated with nephrotic syndrome. Markowitz and colleagues, in 2000, described seven patients—five treated with pamidronate over 90 mg monthly—who subsequently developed nephrotic syndrome and renal failure after over 15 months of therapy (Table 1) [48]. Subsequently, this complication has been reported as early as 4 months, despite the recommended dosage and infusion time [50, 55]. Typical presentations are peripheral edema, hypoalbuminemia, heavy proteinuria, hypercholesterolemia, and frequently various degrees of renal impairment [48]. To date, 19 patients with nephrotic-range proteinuria have been reported; most were patients with myeloma in remission (Table 2). However, in a randomized controlled trial among myeloma patients, in which pamidronate was given to 198 patients and monitored by monthly urianalysis, no patient developed a nephrotic-range proteinuria [75].

In these patients, a unique collapsing focal segmental glomerulosclerosis (CFSG) is often demonstrated [48, 57, 60]. Typically described among young African American patients with human immunodeficiency virus infection, CFSG is a variant of focal segmental glomerulosclerosis, characterized by a marked wrinkling and collapsing of the glomerular basement membrane (Fig. 2) [76]. Electron microscopic examination may show hypertrophy and loss of foot process in podocytes, analogous to the loss of ruffled border observed in osteoclasts treated with bisphosphonates [50, 55]. The high drug concentration achieved in kidney may be responsible for cell-specific toxicities. Finally, it has also been proposed that subclinical injury to the kidney can accumulate after each therapy with bisphosphonate and eventually become clinically evident [55, 77].

Nephrotic syndrome, when accompanied by renal failure, portends a poor prognosis. Only 20% of such patients will

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**Table 2.** Characteristics of patients with nephrotic syndrome associated with pamidronate reported in literature

<table>
<thead>
<tr>
<th>Characteristics of patients and presentations</th>
<th>n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>63 (52–77)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>16 (85)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Langerhan’s histiocytosis</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Number of patients receiving pamidronate greater than 90 mg every 3 to 4 weeks (%)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Median maximum dose of pamidronate among patients receiving pamidronate greater than 90 mg every 3 to 4 weeks* (range)</td>
<td>180 (180–700) mg/month</td>
</tr>
<tr>
<td>Median onset of nephrotic-range proteinuria (range)</td>
<td>20 (4–48) months</td>
</tr>
<tr>
<td>Median maximum proteinuria (range)</td>
<td>12.5 (3.7–28.7) g/day</td>
</tr>
<tr>
<td>Number of patients requiring hemodialysis (%)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Improvement of proteinuria at last follow-up (%)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Pathological diagnosis</td>
<td></td>
</tr>
<tr>
<td>Collapsing focal segmental glomerulosclerosis (%)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis (%)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Minimal change disease (%)</td>
<td>3 (19)</td>
</tr>
</tbody>
</table>

* n = 13; † eight patients on hemodialysis; ‡ n = 16, kidney biopsy performed in 16 patients; one patient had both focal segmental glomerulosclerosis and minimal change disease.
Infusion of bisphosphonates can cause electrolyte abnormalities. Although published data from clinical trials is often limited, in patients with myeloma or those with bone metastasis from breast cancer, pamidronate clearly increases the incidence of hypocalcemia and hypophosphatemia compared with placebo (Table 3) [8, 78]. The incidence of electrolyte imbalances may vary by the underlying disease of the patients. Among breast cancer patients treated in a phase III study of zoledronic acid, hypocalcemia, though often mild, is observed in 39%, compared with 7% in the placebo arm [13]. Moreover, in two randomized trials comparing 4 mg zoledronic acid and 90 mg pamidronate for hypercalcemia of malignancy, the incidence of hypocalcemia approaches 50% with pamidronate and over 50% with zoledronic acid [79]. Hypophosphatemia is most common during treatment of hypercalcemia of malignancy [8]. Hypocalcemia and hypophosphatemia, though usually mild, may lead to serious consequences among susceptible patients. For example, seizure has been reported among patients with brain metastases with mild hypocalcemia; coma has been described in an elderly patient with moderate hypophosphatemia [80, 81].

By far the most well-recognized electrolyte abnormality associated with bisphosphonates is hypocalcemia, which have been extensively described even among patients with hypercalcemia of malignancy [82]. A small comparative trial of ibandronate and pamidronate among patients with hypercalcemia of malignancy indicates that ibandronate maybe more effective, thus associated with an increased rate of hypocalcemia [16]. The onset of symptomatic hypocalcemia varies from a few days after the first treatment to several months after repeated infusion [82–84]. Classic signs, symptoms, and electrocardiographic changes such as peri-oral paraesthesia, tetany, carpopedal spasm, and QT prolongation have been observed, but non-specific lethargy, shakiness, tingling, or weakness can be the only presenting symptoms [85]. Acute pseudogout attack has been reported following rapid normalization of hypercalcemia [86]. Renal impairment and other electrolyte abnormalities, particularly hypomagnesemia, frequently coexist with the hypocalcemia [83, 84].

**Risk factors for hypocalcemia include pre-existing hypovitaminosis D (i.e. due to renal impairment of vitamin D3 production), hypoparathyroidism (i.e. due to previous thyroid surgery or radiation to neck), and hypomagnesemia [85, 87–90]. These conditions impair the normal compensatory mechanism of parathyroid hormone, which can increase renal absorption of calcium and vitamin D3 production in response to a decreased calcium efflux from skeleton after bisphosphonate therapy. Hypomagnesemia also limits the production of parathyroid hormone [91]. Furthermore, concurrent treatment with aminoglycoside or interferon alpha may increase the risk of hypocalcemia due to their inhibitory effect on osteoclasts [61, 92]. Loop diuretics can further worsen hypocalcemia [8]. Finally, widespread osteoblastic metastases may predispose patients to hypocalcemia due to avid calcium uptake into bone [84].

Along with correcting the above precipitating factors of hypocalcemia, replacing calcium, under a close cardiac monitoring in severe cases, is the key to treatment. Supplemening vitamin D empirically has usually been practiced. The recovery from hypocalcemia is prompt; however, some have reported prolonged hypocalcemia up to several months, requiring long-term replacement therapy [82, 88]. Clearly, hypocalcemia can be minimized by strictly adhering to the recommended dosage and interval as high-dose or too short treatment interval increases the risk [93]. Daily calcium and

**Table 3. Pooled incidence of grade III or IV electrolyte abnormalities in three randomized controlled trials for patients with multiple myeloma or bone metastases from solid tumors (adapted from reference [8])**

<table>
<thead>
<tr>
<th>Electrolyte parameters</th>
<th>Placebo (n = 415) Patients (%)</th>
<th>Zoledronic acid 4 mg (n = 973) Patients (%)</th>
<th>Pamidronate 90 mg (n = 537) Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia (&lt;7 mg/dl)</td>
<td>2 (0.5) ×10^-3</td>
<td>13 (1.3) ×10^-3</td>
<td>7 (1.3) ×10^-3</td>
</tr>
<tr>
<td>Hypophosphatemia (&lt;2 mEq/l)</td>
<td>15 (3.6) ×10^-3</td>
<td>120 (12.3) ×10^-3</td>
<td>38 (7.1) ×10^-3</td>
</tr>
<tr>
<td>Hypomagnesemia (&lt;0.9 mEq/l)</td>
<td>1 (0.2) ×10^-3</td>
<td>3 (0.3) ×10^-3</td>
<td>1 (0.2) ×10^-3</td>
</tr>
<tr>
<td>Hypermagnesemia (&gt;3 mEq/l)</td>
<td>10 (2.4) ×10^-3</td>
<td>19 (2.0) ×10^-3</td>
<td>2 (0.4) ×10^-3</td>
</tr>
</tbody>
</table>

×10^-3 n=971; ×10^-3 n=536; ×10^-3 n=535.
vitamin D supplementation is recommended during treatment with zoledronic acid, but hypocalcemia can still occur [8]. Moreover, since patients with pre-existing hypocalcemia are especially susceptible to the development of severe symptomatic hypocalcemia [94], any pre-existing electrolyte imbalances should be treated before initiation of bisphosphonate and regular electrolyte monitoring is recommended [8]. After recovery of hypocalcemia, resumption of treatment may be attempted with a close monitoring of calcium as recurrent hypocalcemia has been reported following re-treatment—despite ongoing calcium and vitamin D supplementation [95].

**Osteonecrosis of the maxilla and mandible**

Osteonecrosis of the maxilla and/or mandible, a condition once endemic among workers of the phosphorus-containing match factories in the 1800s, has now been reported among bisphosphonate-treated patients [96, 97]. Although osteonecrosis of the jaw may occur spontaneously, especially among cancer patients receiving radiation to the head and neck area, these reports typically identify no common association except the use of bisphosphonates, including alendronate, risedronate, pamidronate, ibandronate and zoledronic acid, though so far not with clodronate. To date, over 200 cases have been described since 2003, mostly in multiple myeloma or breast cancer patients (Table 4) [98–119].

Based on a web-based survey of 1203 patients with multiple myeloma or breast cancer, treated with zoledronic acid or pamidronate in the United States, the point prevalence of this complication when excluding patients without a confirmed diagnosis was about 6% [120]. In a retrospective study of myeloma patients from a single institution, the incidence was about 0.4% per patient per year [121]. The major predisposing factors include a previous dental procedure and an underlying dental problem, although this complication has been reported in an edentulous patient [110]. In the two largest series of 63 and 36 patients, about 80% of patients had a preceding dental procedure [98, 102]. Others, however, developed the exposed bone spontaneously, especially near a denture pressure area. Most patients were treated with the recommended dosages of bisphosphonates with the duration ranging from 1 to 94 months. One report described the development of this complication at 9 months after discontinuation of bisphosphonate [110]. Prolonged duration of treatment increase the risk, which is greater with zoledronic acid than with pamidronate, when the treatment goes beyond 36 months [118, 119].

Typically, the patients first present with orofacial pain, described as toothache or denture sore, and trismus. Some experience chronic sinusitis because of oroantral fistula or foul-smelling drainage from cutaneous fistulas [102, 112]. Numbness in the mandible or maxilla may be experienced [108, 109]. In many cases, however, an asymptomatic bony exposure is the only complaint. Examination typically reveals an

### Table 4. Unduplicated publications on jaw complication associated with bisphosphonates

<table>
<thead>
<tr>
<th>Authors, year of publication (reference)</th>
<th>n</th>
<th>Mean age (years)</th>
<th>Diagnosis of myeloma or breast cancer (%)</th>
<th>Preceding dental procedure (%)</th>
<th>Median duration of drug (range in months)</th>
<th>Both mandible and maxilla affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marx, 2003 (98)</td>
<td>36</td>
<td>NR* 35 (97)</td>
<td>28 (78)</td>
<td>NR</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Wang, 2003 (99)</td>
<td>3</td>
<td>58 3 (100)</td>
<td>2 (67)</td>
<td>36 (12–60)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Carter, 2003 (100, 101)</td>
<td>5</td>
<td>71 2 (40)</td>
<td>4 (80)</td>
<td>(6–72)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ruggiero, 2004 (102)</td>
<td>63</td>
<td>62 49 (78)</td>
<td>48 (76)</td>
<td>(6–48)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Lugassy, 2004 (103)</td>
<td>3</td>
<td>66 3 (100)</td>
<td>2 (67)</td>
<td>(48–60)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Estilo, 2004 (104)</td>
<td>23</td>
<td>63† 21 (91)</td>
<td>13 (57)</td>
<td>35 (1–94)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Thakkar, 2004 (105)</td>
<td>14</td>
<td>NR 14 (100)</td>
<td>NR</td>
<td>5 (3–9)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Schuster, 2004 (106)</td>
<td>2</td>
<td>63 2 (100)</td>
<td>NR</td>
<td>84 (84)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Zarychanski, 2004 (107)</td>
<td>4</td>
<td>NR 4 (100)</td>
<td>NR</td>
<td>(18–65)†</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Migliorati, 2005 (108, 109)</td>
<td>18</td>
<td>62 14 (78)</td>
<td>16 (89)</td>
<td>(4–41)†</td>
<td>1 (9)</td>
<td></td>
</tr>
<tr>
<td>Maerevoet, 2005 (110)</td>
<td>10</td>
<td>NR 10 (100)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Vannucchi, 2005 (111)</td>
<td>1</td>
<td>76 1 (100)</td>
<td>1 (100)</td>
<td>36</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bagan, 2005 (112)</td>
<td>10</td>
<td>60 10 (100)</td>
<td>7 (70)</td>
<td>NR</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>Melo, 2005 (113)</td>
<td>1</td>
<td>72 1 (100)</td>
<td>1 (100)</td>
<td>NR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Purcell, 2005 (114)</td>
<td>13</td>
<td>65† 8 (72)</td>
<td>5 (38)</td>
<td>(1–48)***</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Olson, 2005 (115)</td>
<td>1</td>
<td>62 0</td>
<td>1 (100)</td>
<td>29</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Maerevoet, 2005 (116)</td>
<td>9</td>
<td>NR 9 (100)</td>
<td>NR</td>
<td>39 (4–58) for pamidronate, 18 (4–22) for zoledronic</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Lenz, 2005 (117)</td>
<td>3</td>
<td>61 3 (100)</td>
<td>0 (99)</td>
<td>47 (23–72)</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>Ficarra, 2005 (118)</td>
<td>9</td>
<td>62 6 (66)</td>
<td>9 (100)</td>
<td>NR</td>
<td>2 (22)</td>
<td></td>
</tr>
<tr>
<td>Katz, 2005 (119)</td>
<td>3</td>
<td>61 2 (66)</td>
<td>3 (100)</td>
<td>18 (12–24)</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>231</td>
<td>58–76 197 (85)</td>
<td>141 (73)††</td>
<td>(1–94)</td>
<td>14 (8)††</td>
<td></td>
</tr>
</tbody>
</table>

* NR, not reported; † Median duration not reported; † Median; †† Data reported from 11 patients; †† Data reported from 10 patients; ** Data reported from six patients; †† Data reported from 194 patients; †† Data reported from 184 patients.
exposed bone with white, yellow discoloration (Figure 3). The most commonly reported site is the posterior mandible in the area of mylohyoid ridge, but multiple affected sites are common [108, 109]. In a series of 10 patients, the median number of involving sites was two [112]. At times, cervical adenopathy may be present. Probing of the bone may not result in bleeding and the most painful spot appears to be in the surrounding soft tissue [108, 109]. In advanced cases, radiography may demonstrate mottled bone indicating a sequestrum formation [102]. Osteonecrosis of the jaw can also be demonstrated on bone scintigraphy scan, mimicking metastasis. The most commonly isolated organisms are normal oral-cavity flora or Actinomyces [102, 103, 105, 107]. Proposed pathogeneses include vascular insufficiency or inadequate bone turnover—similarly seen in osteoporosis, in which the unique jaw complications are commonly described [98, 100]. Maxilla and mandible are the only bones constantly exposed to external environment via teeth resulting in constant inflammation and high demand of bone turnover, thus increasing its susceptibility to necrosis.

Discontinuation of bisphosphonate is recommended, but new lesions may still develop [98]. Appropriate antibiotics for osteomyelitis, chlorhexidine mouthwash, periodic minor debridement, and wound irrigation have limited the progression of small lesions in most cases. Clindamycin or high-dose penicillin has been commonly used [103, 105–107]. Extensive debridement should be avoided as it may result in further exposure of bone. In the largest report, however, a major surgery was often necessary—sequestrectomy performed in 71%; mandibular or maxillary resection in 25%—primarily due to the inadequacy of minor debridement, pathologic fracture, or oro-antral fistula [102]. The use of flap to cover exposed bone usually results in dehiscence, although rare success has been reported [98, 102]. Covering of the osteonecrosis area with vinyl guards or stints has been suggested [108, 109]. To date, treatment with hyperbaric oxygen has been used in six patients; only one patient experienced an improvement [100–103, 108, 109]. Long-term outcomes of patients with this complication vary, but largely are poor. The two largest case series that provide outcome reports indicate an improvement or resolution in 6–17% of patients, mostly those with limited regions of exposed bones, although long-term follow-up data is limited [104, 108, 109].

Before starting on a long-term bisphosphonate therapy, it is recommended that patients undergo screening dental examination so that any anticipated dental procedures can be carried out well in advance [8, 122]. Patients with dentures should use soft liners. During bisphosphonate treatment, regular dental examination is also suggested and patients who consider any dental procedures or implants involving bone should be advised about the risk of this complication [100]. Orthodontic failure due to cessation of teeth to re-position has been reported during zoledronic acid treatment and thus the procedure should be avoided [123]. If a surgical dental procedure is necessary, some authors propose that bisphosphonate therapy be withheld for a significant period both before and after surgery [100].

**other complications**

Pamidronate has been associated with acquired osteopetrosis in a 12-year-old boy who received high-dose pamidronate for about 3 years for his idiopathic hyperphosphasemia [124]. The child developed bone pain and recurrent fractures, along with elevation of serum BB-CK and acid phosphatase, a hallmark of osteopetrosis. Radiograph showed a sclerotic skull; dual-energy x-ray absorptiometry showed a marked increase in bone mineral density; and a bone biopsy showed a delayed removal of calcified primary spongiosa. Despite the discontinuation of pamidronate, no improvement was seen. Excessive and prolonged treatment with pamidronate may have compromised the bone quality despite the increase in bone density.

An allergic skin reaction has been described in association with pamidronate [125]. Observed in less than 1% of patients, the reaction is reproducible and may happen after the first or subsequent infusions, as early as minutes after or as late as 4 days afterward. Complete resolution occurs with supportive care and switching to clodronate or alendronate has been successful. Pamidronate has also been linked to ototoxicity, characterized by tinnitus, hearing loss, and vertigo, but the causal relationship remain unclear [126]. Boumans and colleagues described two patients, who had stapedial otosclerosis treated with pamidronate, developed severe irreversible bilateral hearing loss a year later. Reid and colleagues described a patient with Paget’s disease treated with high-dose pamidronate who developed bilateral high-tone sensorineural hearing loss and hypofunction of the vestibular apparatus, which resolved 9 months after discontinuation of pamidronate, but the tinnitus persisted.

Finally, thrombotic thrombocytopenic purpura and acute tumor lysis syndrome have been reported in patients receiving zoledronic acid, although the causal relationship cannot be ascertained [127, 128].

**comments**

Evidence of both common and uncommon side effects of intravenous bisphosphonates continues to accumulate. While
there are many associations, a systematic establishment of causal relationship between the drugs and side effects has not been possible for all complications. Nevertheless, in general, they are well tolerated. Of the three commonly used intravenous bisphosphonates (pamidronate, zoledronic acid, and ibandronate), ibandronate has been least reported in association with renal side effects in literature to date. We recommend that, before prescribing any intravenous bisphosphonates, risks and benefits must be weighed carefully by both physicians and well-informed patients.

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