Incidence of serious side effects with intravenous bisphosphonate: a clinical audit

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Summary

Background: Bisphosphonates (BP) have been associated with osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). The prevalence of these side effects in intravenous (IV) BP-treated subjects is not well understood.

Aim: This audit aimed to delineate the prevalence of ONJ, thigh pain and AFF in patients having regular IV BP and its effect on bone mineral density (BMD).

Design and Methods: Patients attending for IV BP over a 3-month period completed a questionnaire about thigh pain and dental health. Data concerning BMD, treatment indication and treatment history were obtained from medical records.

Results: There were 201 patients between 28 and 94 years (74.1% female) mostly on zoledronate (ZOL) (102) or pamidronate (PAM) (97). Osteoporosis (75.6%) and Paget’s disease (16.5%) were the main indications for treatment; median length of IV BP was 4 years (range 0.25–25). One patient had ONJ (0.5%) while oral pain was reported by 6.5% and 12.7% noted tooth loosening. Twenty-seven subjects (13.4%) complained of current thigh pain. AFF occurred in four patients (2%), none of whom had idiopathic osteoporosis. At time of AFF, only one patient had a femoral neck T-score less than −2.5. All four had received pamidronate treatment; median 12.5 years (range 7–22). IV BP treatment significantly increased lumbar spine BMD but not femoral neck BMD.

Conclusions: Classical ONJ was rare (0.5%), although tooth loss was more frequent. Thigh pain was frequent while AFF occurred in 2.0% of subjects and was associated with long treatment periods and non-osteoporotic bone.

Introduction

Bisphosphonates (BP) are widely used to treat a number of different medical conditions including osteoporosis1 and, particularly intravenous (IV) BP, to treat other conditions affecting bone both benign2 and malignant.3 However, in the past 10 years there have been reports of side effects with treatment including osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF).

In 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) provided advice on ONJ. The risk of developing ONJ with oral BP was low but is substantially greater for patients receiving IV BP, particularly for cancer. It was recommended that during treatment, patients should be reminded to maintain good oral hygiene, have routine dental check-ups and report any oral symptoms such as dental pain and swelling.4
The MHRA also advised that atypical stress fractures of the proximal femoral shaft have been reported in patients treated long term with Alendronic acid. The American Society for Bone and Mineral Research set up a task force to define and characterize these fractures. AFF are transverse or oblique fractures that occur mainly in the subtrochanteric region with little or no trauma. These fractures have been reported in both untreated and BP-treated subjects, but reports suggest they are more common in subjects on long-term BP treatment. AFF are transverse or oblique fractures that occur mainly in the subtrochanteric region with little or no trauma. These fractures have been reported in both untreated and BP-treated subjects, but reports suggest they are more common in subjects on long-term BP treatment. Subtrochanteric fractures are rare accounting for ~5% of all hip fractures, but are more common in females than males and increase with age. A small but significant increase in the rate of subtrochanteric fractures in women has been reported between 1999 and 2007 in the USA, a period in which BP use also increased.

The incidence of ONJ and of AFF during long-term use of IV BP for non-malignant conditions is not well defined. ONJ has been reported in 6–10% of subjects receiving IV BP for malignant disease. However, BP dosages are higher than used in treatment for benign conditions and adjunctive treatment such as chemotherapy is also given. Despite lower incidences in osteoporosis, ONJ has been reported as occurring as little as 1 month after starting both oral and IV BP therapy. The shorter mean duration until ONJ occurrence, 6 months, with IV BP treatment compared with 12 months for oral BP suggested that IV BP treatment might give rise to problems earlier. The appearance of AFF with oral treatment after as little as 1.5 years despite only ~1% of oral BP being absorbed also suggested that IV BP could give rise to problems earlier. We thus audited 201 patients attending our IV BP service over a 3-month period. The primary aim of the audit was to determine the frequency of ONJ and AFF in consecutive patients while secondary outcomes were to examine the incidence of thigh pain and confirm treatment benefit on bone mineral density (BMD) levels.

Materials and methods

In 2011, 899 subjects were being given IV BP for benign conditions, including Zoledronate (ZOL), Pamidronate (PAM) and Ibandronate in a variety of dosing regimens. Data were collected on a subpopulation of 201 consecutive patients attending the hospital for IV BP either as an in-patient or as a day case between 29 November 2010 and 25 February 2011. The 3-month period was chosen as it generated a random subpopulation that was not biased for BP treatment length or dosing regimen. The study was an audit of a clinical service and informed consent was therefore not required.

On attendance for IV BP treatment, patients were asked to complete a questionnaire on side effects including thigh pain and dental health. In accordance with our current clinical protocol, since 2010 any patient who reported thigh pain on attendance had bilateral femoral radiographs to exclude atypical fracture. In conjunction with the patient questionnaire, we also conducted a review of the patients’ bone health status. Information collected included indication for treatment, treatment history and BMD. If available, BMD data from their initial assessment, prior to IV BP initiation and their latest clinic appointment were recorded. Apart from the patient questionnaire, all data were obtained from the patients’ medical records.

BMD was measured using dual energy X-ray absorptiometry (DXA) at the lumbar spine (LS; L2–4) and femoral neck (FN) with a Hologic densitometer (Hologic Inc., Bedford, MA, USA) QDR1000 (1988–98) or a QDR 4500 (1998–present). BMD T-scores were calculated [(individual result–peak bone mass Mean) /peak bone mass Standard Deviation (SD)] for each site using the current Hologic reference levels for LS and NHANES reference levels for FN.

Statistics

Data were analysed using SPSS v17 [SPSS (UK) Ltd, Woking, UK]. Differences within the audit population were analysed by the Mann–Whitney U-test if the data were non-parametric or Chi-squared tests for discontinuous data. Paired Wilcoxon signed-rank test was used to examine the effect of BP treatment on BMD data over time.

Results

Data were collected from 149 females and 52 males aged between 28 and 94 years (Table 1). The majority of the patients were either on ZOL (n = 102) or PAM (n = 97). Females were more likely to receive ZOL than PAM while for males the opposite was true (χ² P<0.001). The main reason for receiving BP treatment was osteoporosis for both males and females (Table 1), but Paget’s disease of bone accounted for a significantly higher proportion of males than females (19 versus 1%; χ² P<0.001). Of the 201 patients, 44.7% (n = 90) subjects did not receive or were unable to tolerate an oral BP. There were no significant differences between the genders in regard to co-morbidities.
Time on BP

The median time on BP treatment was 7 years in total, including any previous oral treatment. The total number of patient years on any BP treatment was 1477 patient years. Men had been on treatment for longer with a median duration of total BP treatment of 8.5 years compared with 7 years for females ($P<0.05$). The median time on IV treatment was 4 years [7.5 years in men and 3 years in women ($P<0.001$)] with a total of 1092 patient years of IV BP treatment. Median length of total BP treatment was 9 years for PAM and 5 years for ZOL ($P<0.001$) and for IV treatment was 7 years for PAM and 2 years for ZOL ($P<0.001$).

Dental health

During the audit, one patient (0.5%) on IV BP reported a diagnosis of ONJ as defined by the MHRA as made by a maxillofacial surgeon in 2010. The patient was asymptomatic and had received 15 years of BP treatment for osteoporosis prior to spontaneous development of ONJ. The incidence of ONJ in this population was 9/10 000 patient years of IV BP or 6.8/10 000 patient years of total BP treatment.

Most patients (73%) reported a dental check-up prior to starting an IV BP. A total of 87% of the patients were registered with a dentist and 74% had visited a dentist in the last year; however, 43 patients were unsure if their dentist knew they were on a BP. There were 87 patients who had a dental procedure performed while on IV BP including 44 extractions, 54 fillings, 4 root treatments and 14 other procedures. Since the MHRA highlighted dental mobility, pain and swelling, we also enquired about these features. Tooth loss was reported in 12.7% of the subjects, while 6.5% of the subjects had suffered from pain and swelling of the mouth, 1% had suffered numbness of the jaw and 20% reported mouth ulcers.

Thigh pain

There were 74 subjects (36.8%) who reported suffering from thigh pain at some point during the course of their BP treatment. However, during the 3-month audit period, current thigh pain was reported by 27 subjects (13.4%) from whom bilateral femoral radiographs were obtained.
Atypical femoral fractures

From the 27 bilateral femoral radiographs, 3 patients with 4 AFF were identified. One additional subject reported having had bilateral femoral stress fractures previously which on review showed features consistent with AFF. Therefore, four subjects (2%) with six AFF were identified during the audit. The incidence of AFF cases in the audit population was 36.6/10,000 patient years of IV BP or 50.7/10,000 patient years of PAM: no atypical fracture occurred in the ZOL group.

The characteristics of the four AFF subjects are shown in Table 2. None of the AFF cases were being treated for idiopathic osteoporosis or Paget’s disease. The two cases being treated for osteogenesis imperfecta were related and both had bilateral AFF. Only one subject exhibited osteoporosis at the FN. All of these subjects had been on long-term PAM for a median of 12.5 years and had experienced prodromal pain prior to fracture but the relationship between pain and fracture development is unknown. In Case 4, pelvic radiographs had been taken for unrelated reasons in 2005 (Figure 1A) and 2008 (Figure 1B). In 2005, no femoral cortical elevation was apparent in the left femur but cortical elevation was present (and asymptomatic) by 2008 but was not reported as abnormal at the time. When the patient attended for PAM in 2010 during the audit, she gave a history of thigh pain for 3 months. A further X-ray (Figure 1C) and technetium scan in 2010 showed the presence of an atypical subtrochanteric fracture of the left femur in the region of the cortical thickening.

BMD data

The BMD data (Table 3) indicate that at the latest assessment IV BP was associated with a significant increase in LS BMD from initial assessment (0.842 versus 0.769; \(P<0.001\)) and from pre-IV treatment levels (0.823 versus 0.800; \(P<0.001\)). Overall, FN BMD showed little change on BP treatment, with 50% of subjects showing an increase in BMD from initial assessment.

Proportions of patients who were osteoporotic (T-score less than \(-2.5\)), osteopenic (T-score \(-2.5\) to \(-1\)) or normal (T-score greater than \(-1\)) at baseline and the latest BMD are shown in Table 4. At the LS, the number of osteoporotic subjects decreased from 59.3% baseline to 42.3% at the last assessment.

Table 2 Characteristics of the atypical fracture group

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Reason for treatment</th>
<th>Years on PAM</th>
<th>Total dose (mg)</th>
<th>Prodromal pain</th>
<th>Bilateral</th>
<th>Last FN T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>F</td>
<td>Failed spinal fusion</td>
<td>12</td>
<td>3630</td>
<td>Y</td>
<td>N</td>
<td>-0.94</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>F</td>
<td>Osteogenesis imperfecta</td>
<td>8</td>
<td>2010</td>
<td>Y</td>
<td>Y</td>
<td>-1.3</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>Osteogenesis imperfecta</td>
<td>13</td>
<td>4170</td>
<td>Y</td>
<td>Y</td>
<td>-4.3</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>Osteitis pubis</td>
<td>22</td>
<td>8130</td>
<td>Y</td>
<td>N</td>
<td>-0.96</td>
</tr>
</tbody>
</table>

Figure 1. Radiological time course of atypical fracture development. (A) Radiograph from 2005 showing no obvious abnormality. (B) Radiograph from 2008 showing area of cortical expansion on the left femur (indicated by white arrow). (C) Radiograph from 2010 showing enlarged area of cortical expansion (indicated by white arrow).
Discussion

Our results show that the majority of patients included in this audit were receiving IV BP for either osteoporosis or Paget’s disease of bone, with a small number of other conditions including osteogenesis imperfecta and steroid therapy.

Most patients had acted in accordance with MHRA recommendations for dental checks. The audit population did report some dental problems particularly mouth ulcers but also a small number suffered from pain and swelling in the mouth. Only one case of ONJ (0.5%) was found in the audit: this occurred spontaneously and the lesion healed with continued BP use. Since this was a clinical audit of IV BP-service subjects, we had no control group for comparison to determine if the dental health was worse than in the general population. The incidence of ONJ in osteoporotic subjects has not been fully established but rates of < 1/15 000 patient years for ZOL15 and > 1/100 000 patient years in osteoporosis patients have been reported.10 The incidence was much higher in this report due to the small sample size.

Four-fold more subjects (2%) were found to have had an AFF than had ONJ (0.5%) during the audit. All of the AFF subjects were receiving PAM, two for non-osteoporotic conditions while two patients had osteogenesis imperfecta. A small study of asymptomatic patients on oral BP for a mean of 7.95 years also found that 2% of subjects had an AFF.16 Incidence rates of 0.09–13 femoral fractures per 10 000 patient years have been reported in subjects not on a BP17–19 compared with 0.2–31/10 000 patient years in those on a BP.19–21 In our study we found a higher level of incidence, 51/10 000 patient years compared with the 31/10 000 patient years reported in a Danish cohort on alendronate.17 However, comparisons between studies are difficult due to differences in methodology, treatment duration and lack of radiographic verification. These differences in incidence rates may reflect differences in compliance. The majority of studies have used prescription databases to determine BP use and have included patients with limited prescription refills.

The duration of BP use has been associated with an increased risk of subtrochanteric fracture,19 with increased risk reported after >5 years of BP treatment.22 A systematic review of 31 published reports found that 85% of cases were on alendronate with a median duration of treatment of 5 years (range 0.25–16 years).23 In this report, the median duration of PAM treatment at first fracture was 12.5 years (range 8–21 years). This suggests that long-term IV BP is no more likely to lead to AFF than oral BP treatment. AFF have also been reported in patients treated with other osteoporosis medications.

While there was a corresponding increase in the number of subjects who were either osteopenic or had normal BMD. At baseline, 34.6% of subjects were not osteoporotic at either the LS or FN, this proportion increasing to 46.5% by the last BMD measurement.

### Table 3
BMD levels in the audit population at baseline, pre- and post-IV BP treatment

<table>
<thead>
<tr>
<th></th>
<th>LS BMD (g/cm²)</th>
<th>FN BMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>Initial assessment</td>
<td>(0.706–0.860)</td>
<td>(0.529–0.677)</td>
</tr>
<tr>
<td>Pre-IV BP</td>
<td>0.791</td>
<td>0.575</td>
</tr>
<tr>
<td>P-value</td>
<td>0.035</td>
<td>0.022</td>
</tr>
<tr>
<td>n</td>
<td>136</td>
<td>151</td>
</tr>
<tr>
<td>Initial assessment</td>
<td>(0.700–0.901)</td>
<td>(0.545–0.693)</td>
</tr>
<tr>
<td>Last assessment</td>
<td>0.842</td>
<td>0.614</td>
</tr>
<tr>
<td>IV treatment</td>
<td>5 (0.25–21)</td>
<td>5 (0.25–21)</td>
</tr>
<tr>
<td>length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>0.773</td>
</tr>
</tbody>
</table>

Results shown are median (IQR).

### Table 4
Proportions of osteoporotic, osteopenic and normal BMD patients in the audit population

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Latest BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS</td>
<td>FN</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Osteoporotic</td>
<td>112 (59.3)</td>
<td>66 (42.3)</td>
</tr>
<tr>
<td>Osteopenic</td>
<td>49 (25.9)</td>
<td>51 (32.7)</td>
</tr>
<tr>
<td>Normal</td>
<td>28 (14.8)</td>
<td>39 (25)</td>
</tr>
</tbody>
</table>

Table 3: BMD levels in the audit population at baseline, pre- and post-IV BP treatment

Table 4: Proportions of osteoporotic, osteopenic and normal BMD patients in the audit population
including raloxifene, calcitonin and teriparatide at rates similar to BP-treated subjects\(^20,24\) and an increase in incidence rates in the year before initiation of BP treatment has been reported.\(^25\) Therefore, further work needs to be done to elucidate the role of the disease or bone quality from the effect of treatment in the mechanism of AFF development.

BMD data in atypical fracture are limited: of the 141 cases included in a systematic review, only 50 had BMD data, of these 26% were osteoporotic while 56% were osteopenic.\(^23\) We also found a higher proportion of osteopenic (75%) than osteoporotic (25%) patients with AFF in this audit. The AFF patients in this audit did not have idiopathic osteoporosis, and thus non-osteoporotic patients may be at greater risk of these fractures and may require more oversight. Our data do not give a clear indication of the frequency of radiography needed to detect these fractures, though in Case 4, 3 years separated a normal radiograph from an abnormal appearance, and another 2 years elapsed before symptoms appeared.

The limitations of this study include limited numbers and difficulty in obtaining information regarding prior oral bisphosphonate usage and adherence. Since this was a clinical audit, we were unable to collect data from an untreated control group for comparison. Dental health has improved over time and a comparator group would have been useful in determining the impact of BP on the prevalence of oral symptoms in the elderly. Only those patients who were currently symptomatic underwent radiographic examination and therefore the incidence of AFF may be underreported in this population.

In conclusion, five cases of side effects, one ONJ (0.5%) and four AFF (2.%) were identified in the clinical audit. All of the AFF cases were observed in patients on PAM, an incidence of 51 cases/10 000 patient-years. The majority of cases were osteopenic (75%) and had been on treatment for 12.5 years prior to the first fracture. The incidence rate is higher than the majority of previous reports; however the time taken to fracture was much longer. Since radiological features of AFF may exist in the absence of pain, regular radiographic monitoring of the femora of subjects on IV BP may be of use to identify subjects developing AFF. Further work needs to be done to ascertain the optimum interval for monitoring.

Conflict of interest: None declared.

References


