Fibrous dysplasia of bone in adults is a rare anomaly of skeletal development caused by a defect in differentiation of osteoblasts. This condition is associated with bone pain, bone deformity, and an increased incidence of fracture. Involvement of the skull is associated with headache along with dysmorphic features. Until recently, the principal treatment has been resection or fracture repair, although the latter is often palliative at best. However, a new insight into the molecular mechanism of fibrous dysplasia has led to the use of bisphosphonates to treat this disease.

The authors examined the effects of high-dose oral alendronate (40 mg daily) for 6 months on 3 adult patients with intractable headache due to fibrous dysplasia of the skull. Each patient had disease processes not amenable to surgery. The patients underwent clinical follow-up at 1, 3, and 6 months. Their pain levels were documented at each visit by using a visual analog scale. All 3 patients demonstrated a significant decrease in pain levels and became independent of scheduled analgesics. Tumor bulk did not progress during this interval in any patient. Overall, alendronate was well tolerated, although in 1 patient it was discontinued early due to esophagitis. High-dose oral bisphosphonate therapy is an alternative therapeutic option for the palliative treatment of patients with fibrous dysplasia of the skull.

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Key Words • alendronate • bisphosphonate • fibrous dysplasia • palliation • skull

Much of what is known about the molecular mechanism of fibrous dysplasia is derived from studies of patients with McCune–Albright syndrome, a disorder primarily found in children, characterized by the classic triad of polyostotic fibrous dysplasia, café-au-lait spots, and peripheral precocious puberty. Various forms of activating mutations in the gene encoding the α subunit of Gs, the G protein that stimulates adenylyl cyclase activity, have been identified. In a European study, the mutation was identified in blood samples from 46% of patients who presented with the classic triad. Moreover it was found in 90% of patients in whom affected tissue could be removed for biopsy. The increased Gs activity in osteoblastic progenitor cells is postulated to result in their increased proliferation and abnormal differentiation. Studies have also established a link between the Gs-alpha mutation and an increase in bone stromal cell interleukin-6 production, which may promote osteoclast activity. Thus, the complex pathogenesis of fibrous dysplasia is thought to arise from an imbalance of bone formation and destruction.

Bisphosphonates are drugs often used in the management of osteoporosis, hypercalcemia of malignancy, and metastatic disease to bone. They reduce osteoclast activity...
by attaching to bone surfaces, especially those undergoing active resorption, serving as a biochemical barrier to bone resorption.\textsuperscript{5,12} The use of high-dose bisphosphonates in Paget disease, a bone disorder characterized by excessive osteoclast activity, is well established.\textsuperscript{6} Because this disease shares mechanistic similarities with fibrous dysplasia, high-dose bisphosphonates have recently been used to treat fibrous dysplasia. There have been several case series involving intravenous administration of high-dose bisphosphonates in patients, to reduce pain and tumor burden from fibrous dysplasia, with generally positive results.\textsuperscript{2,4,12–14,16} However, there are limited reports of oral bisphosphonates for this purpose.

In this case series, we report the preliminary, clinical response of skull-based fibrous dysplasia to high-dose oral alendronate. We demonstrate that oral alendronate is efficacious in reducing pain in such patients.

**Methods**

Patients with fibrous dysplasia were recruited from the neurosurgery clinic. These patients were considered poor surgical candidates given the extent and location of disease, and all received scheduled analgesics for pain relief. Patients with a history of peptic ulcer disease, gastroesophageal reflux, and esophagitis were excluded. Oral alendronate was administered at a daily dose of 40 mg for 6 months, the regimen often used for treatment of Paget disease. The level of pain was documented using a visual analog scale at the time of each clinic visit. More than 70% of the maximum score was considered “severe,” 30–70% “moderate,” and < 30% “mild.” The patients underwent follow-up at 1-, 3-, and 6-month intervals. At each visit, pain score, subjective reports on functionality, and side effects were noted. Analysis consisted of descriptive comparisons of pain scales during alendronate administration.

**Results**

Three patients were recruited for the study. Clinical data are summarized in Table 1. All patients described severe pain at the initiation of alendronate therapy.

By 2 months, all patients had significant reduction in pain; it was virtually absent at 6 months in 2 and mild in the other. Alendronate was well tolerated. The patient in Case 2 developed mild substernal burning consistent with esophagitis at 4 months, and alendronate was discontinued. The symptoms resolved within a week. She remained pain free for 15 months, when she described resumption of her headaches. Alendronate was cautiously restarted at the same dose, and after 1 month she noted improvement in her headaches, without side effects. There was no evidence of fibrous dysplasia growth during the 6 months.

**Case Reports**

**Case 1**

This 31-year-old developmentally delayed man was found to have an osseous growth in his occiput, and biopsy confirmed fibrous dysplasia. He subsequently developed left orbital proptosis and presented to us with severe left frontal headaches, requiring scheduled narcotic analgesic use. A CT scan showed abnormal bone remodeling and thickening around the left supraorbital area, inferiorty displacing the ipsilateral orbit, anterior clinoid, frontal and paranasal sinuses, ethmoid sinus, and inferior turbinate (Fig. 1). The patient did not wish to undergo complex reconstructive surgery.

On physical examination, the patient exhibited several features of developmental delay, proptosis of his left eye, and tenderness on palpation to the left frontal area. There were no other areas of bone pain.

A regimen of daily alendronate was initiated. No other adjustments were made to the patient’s outpatient drug regimen, and he received no other treatment for his disease. At his 3-month follow-up visit, he noted that his headaches improved such that he only remembered a few days of severe headache in that time period. He tolerated the high-dose treatment well without side effects. At his 6-month clinic visit, he rated his overall pain to be mild on a visual analog scale and his analgesic agents had been discontinued. A CT scan demonstrated that the left orbital bone changes were stable (not shown).

**Case 2**

This 43-year-old woman presented with constant, severe frontal headaches and general complaints of malaise and lightheadedness. Her MR image revealed an abnormal clival bone, which, as determined on a CT scan, was consistent with fibrous dysplasia. She had no hormonal abnormalities or changes in her vision.

Her examination was unremarkable, and her skull was of normal shape. There was no clinical evidence for hypopituitarism. Her visual fields were full. She had no trigger points for her frontal headaches.

Based on the radiographic findings and her complaint of headache, she was started on alendronate. She reported dramatic improvement in her headaches at her 3-month follow-up visit (rated mild on visual analog scale). Within 2

**TABLE 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Location of Skull Involvement</th>
<th>Pain Level Pretreatment</th>
<th>6 Mos Posttreatment</th>
<th>Complications</th>
<th>Follow-Up Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31, M occiput, lt orbit, anterior clinoid, frontal, paranasal, &amp; ethmoid sinuses</td>
<td>severe</td>
<td>mild</td>
<td>none</td>
<td>3 yrs</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>43, F clivus</td>
<td>severe</td>
<td>none</td>
<td>esophagitis</td>
<td>18 mos</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>58, M sphenoid sinus</td>
<td>severe</td>
<td>mild</td>
<td>none</td>
<td>6 mos</td>
<td></td>
</tr>
</tbody>
</table>
months, she was able to return to work after having been on disability for more than a year. At 4 months, she developed mild substernal burning, and, because of concern of the presence of esophagitis, the alendronate was discontinued. At her 6-month follow-up visit, she remained pain free.

Case 3

This 58-year-old man presented to us after several weeks of headache and double vision. An MR image revealed a lesion within his sphenoid sinus. He underwent a biopsy procedure via a transsphenoidal approach, and at surgery the sphenoid bone was found to be solid and firm, with a fibrous component and hyperostotic changes. The biopsy was consistent with fibrous dysplasia. Extensive resection was not done to avoid devastating neurological sequelae, given the proximity of the lesion to the internal carotid arteries and cavernous sinuses. He did not receive postoperative radiation therapy and was followed up conservatively with serial MR images.

His headaches worsened over time without obvious progression of his sphenoid lesion. Given that further surgery was deemed too high of a risk, he was placed on a trial of alendronate without changing any other medication. At his 6-month follow-up visit, his headaches had substantially decreased (from severe to mild), without any side effects.

Discussion

In this case series, we describe palliation of head pain from fibrous dysplasia of the skull by using high-dose oral alendronate therapy in 3 patients. Six months of treatment resulted in dramatic reduction of headache. Overall, alendronate was well tolerated. Furthermore, there was no evidence of tumor growth during the study period.

There are limited therapeutic options beyond surgery and pain medications. High-dose intravenous bisphosphonates have been given to patients with fibrous dysplasia since the 1990s, and palliation has been observed in a subset of such patients. In a series published in 1994, 9 patients were placed on a regimen of intravenous pamidronate (180 mg every 6 months), and all demonstrated striking radiographic improvement as well as reduction in bone pain. Since then, several groups have studied the long-term effects of this intravenous bisphosphonate regimen in a larger patient population with similar results. In one study, 58 patients treated with intravenous pamidronate were followed up for an average of 50 months. Pain intensity was reduced by 41% after the first treatment. The authors saw an additive palliative effect (69% reduction) with subsequent treatment cycles. Half of the patients showed increased filling of osteolytic lesions and/or cortical thickening on plain radiographs. The majority of these patients had disease affecting the hip and long bones. The results were similar in adults and children, the latter of which composed ~30% of the study population.

Other studies regarding administration of intravenous pamidronate at 6-month intervals have also demonstrated favorable outcomes as measured by pain scales, hip bone mineral density, or biochemical markers of bone turnover (such as total alkaline phosphatase, serum osteocalcin, and type I collagen C-terminal breakdown products). Although there have been no published randomized, prospective trials to date, there is mounting evidence from open label studies and ongoing placebo-controlled trials that intravenous bisphosphonates relieve bone pain in patients with fibrous dysplasia. The effect of oral bisphosphonates in such patients, however, has been only sparsely reported.

The general safety profile of oral alendronate has been shown to be satisfactory. However, there has been recent rising concern for the risk of mandibular necrosis. In one study, the frequency in patients with Paget disease was 0.26%; however, this increased to 1.8% if tooth extractions were done while the patient was taking the medication. Most studies have reported that this side effect is far less common with oral therapy than with intravenous therapy. Current recommendations for safe drug administration suggest that patients should be in good dental health prior to starting bisphosphonates.

In our study group, alendronate was discontinued in 1 patient because of esophagitis symptoms. Esophagitis is a known complication of oral bisphosphonate therapy, and, fortunately, our patient remained pain free after the drug was discontinued. Otherwise, no other adverse effects, including severe bone pain, mandibular necrosis, abdominal discomfort, vomiting, diarrhea, or gastrointestinal bleeding, were reported.

In conclusion, we have demonstrated effectiveness of oral bisphosphonate therapy in the palliative treatment of headache from fibrous dysplasia of the skull in a small number of patients. Furthermore, there was no evidence of...
tumor growth during the follow-up period was short. In 1 patient, the medication was discontinued early, but her pain did not return. Clearly, double-blind, placebo-controlled, randomized trials are necessary to demonstrate further that high-dose oral bisphosphonates are effective at reducing pain and controlling tumor bulk. Such studies could also serve to determine the value of prognostic factors, such as measurement of bone turnover markers and extent of disease. In the meantime, our study supports consideration of high-dose oral bisphosphonates for the palliative treatment of bone pain in adults with fibrous dysplasia in an outpatient setting.

**Disclaimer**

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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