Clinical Note

Treatment of Chronic Mechanical Spinal Pain with Intravenous Pamidronate: A Review of Medical Records

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Abstract
We explored the effect of intravenous infusions of a bisphosphonate, pamidronate, in the management of chronic mechanical spinal pain, a worldwide public health problem in terms of lost workdays, medical treatment costs, and suffering. Bisphosphonates have an anti-nociceptive effect in animals. In humans, intravenous pamidronate relieves numerous painful conditions, including metastatic bone pain, ankylosing spondylitis, rheumatoid arthritis, and complex regional pain syndrome. We reviewed the charts of 25 patients who had experienced disabling spinal pain for several years, and whom we treated with intravenous pamidronate. None had a history of osteoporotic vertebral fractures or metastatic disease. Pain rating scores decreased in 91% of patients: on a 0–10 numeric rating scale, the mean pain change was −3.6 points and mean percentage change was −41% (P < 0.0001). There was no increase in opioid or nonopioid analgesic medications associated with pain relief. The apparent analgesic effect of pamidronate for chronic mechanical spinal pain needs to be confirmed with placebo-controlled trials. J Pain Symptom Manage 2003;26:678–683. © 2003 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Pamidronate, chronic back pain, analgesia, neck pain, spinal pain

Introduction
Chronic back pain, while nonfatal, is an extremely prevalent, often disabling, worldwide public health problem. About 59–85% of all people have back pain at some time in life. In 1988, spine and back impairments in the United States accounted for over 185 million days of restricted activity, including 83 million days confined to bed. The annual productivity dollar loss from chronic backache is approximately $20–50 billion, and the medical cost associated with treating this chronic illness is $20–150 billion.

Typically, patients with chronic mechanical back pain associated with spondylotic disease...
have had intermittent, well-localized spinal pain with variable intensity for 10 years. Most have consulted many health care providers, have undergone a variety of treatments, and have used numerous pain medications in their search of a means to alleviate pain. A few have been subjected to aggressive treatment measures, including surgery.

Pamidronate is a bisphosphonate that has been shown to provide analgesia for metastatic bone pain. Its analgesic effects have also been widely documented in a variety of noncancer painful states including ankylosing spondylitis, rheumatoid arthritis, and other inflammatory articular conditions. Most recently, pamidronate was shown to benefit patients with complex regional pain syndrome; pain was totally alleviated in 25 of 29 (86.2%) cases. Pamidronate also has been found to decrease animal nociceptive behavior in experimental models of mechanical and chemical pain.

We were motivated to explore the use of pamidronate on a compassionate basis in patients with debilitating, chronic spinal pain of noncancer origin because of the proven analgesic properties of this drug, as well as the likelihood of an overlap between the mechanisms responsible for noncancer spinal pain and cancer spinal pain, the condition for which pamidronate is most widely used. Although in some cases of cancer spinal pain, both neuropathic and nociceptive mechanisms may play a role, bone pain caused by metastases is commonly regarded as a pain of mechanical/nociceptive nature, especially if pathological fractures are present. Likewise, axial back pain (i.e., without clinically relevant pain of radiculopathic origin) in the presence of spondylotic disease (but not other specific diseases or etiologies known to cause back pain) has also been regarded as a mechanical/nociceptive type of pain.

In patients with metastatic bone pain, the analgesic effect of pamidronate appears to be prompt, namely, within a matter of weeks. This time of onset suggests that pamidronate’s acute analgesic action cannot strictly be related to its well-known anti-osteoporotic effect, but likely to other still undetermined potential mechanisms. Further, the nonspecificity of pamidronate with regard to type of cancer, its reported analgesic effect for noncancer bone pain, and for non-bone pain in animals, suggest that pamidronate may provide analgesia for a broad spectrum of conditions. It is against this backdrop that we report our experience with pamidronate for the treatment of debilitating, chronic, mechanical spinal pain in patients with no history of metastatic bone disease or osteoporotic vertebral fractures.

Methods

Subjects

We received approval from the Institutional Review Board of the New York University School of Medicine to conduct a review of the medical records of 25 patients with disabling, chronic spinal pain who had come to the Comprehensive Pain Treatment Center (CPTC) of the Hospital for Joint Diseases Orthopaedic Institute, Mount Sinai–NYU Health, in New York City, between February 15, 2001, and August 15, 2001. The treated patients were affected by degenerative spondylotic disease, and presented with the chief complaint of chronic axial spinal pain. None of the patients had a history of dementia, hypocalcemia, renal disease, or liver disease.

Pamidronate Infusion Intervention

Prior to the infusion, all patients underwent routine blood tests including a comprehensive metabolic panel, thyroid function tests, and assessment of calcium and magnesium serum levels. A solution containing 90 mg of pamidronate dissolved in 10 cc of sterile water and 250 cc of 5% dextrose solution was infused intravenously over 4 hours. Vital sign assessments and assessment for side effects were performed within 30 minutes after the start of the infusion and at completion of the treatment. The patients received a series of monthly intravenous pamidronate infusions on a compassionate and empirical basis. All patients were scheduled to receive at least three infusions within a period of three months. In order to prevent or minimize post-infusion hypocalcemia, we recommend that our patients take approximately 1,000 mg of a calcium oral supplementation per day throughout the treatment period. Further, patients underwent follow-up blood tests, including calcium and magnesium serum levels, within 2 weeks post-infusion.

Before starting treatment, we informed our patients that they might experience “flu-like”
symptoms (i.e., myalgias and/or fever,) for two to three days after each infusion. After treating the initial 6 patients, we began to recommend as part of our treatment protocol the use of acetaminophen 500 mg or ibuprofen 400 mg three times a day from the day of the infusion through two days post-infusion. This treatment protocol precaution was found to be useful in improving patients’ compliance with their subsequent pamidronate infusions.

Outcome Measures and Statistical Analysis

Patients were asked to rate their pain on a 0–10 numeric rating scale (NRS), where 0 indicates no pain, and 10 indicates the worst pain imaginable. Differences between pain intensity levels at baseline (before the first infusion) and post-treatment (after the last infusion), and percentage differences of these scores (i.e., $100 \times \left[ \frac{\text{baseline pain score} - \text{pain score after final treatment}}{\text{baseline pain score}} \right]$) were analyzed with the $t$ test for matched pairs, using the SAS MEANS procedure. Relationships of pain changes to sex and ethnicity were evaluated with the TTEST procedure, and correlations between pain changes and age with the CORR procedure.

Results

Twenty of the 25 patients (80%) were female. Fourteen (56%) were white, 5 (20%) were Hispanic, and 3 (12%) were black. The median age was 54 years (range: 41–84), and the median duration of pain was 5 years (range: 1–20 years). Prior to seeking treatment at the CPTC, the patients had undergone numerous procedures, including radiographs (including flexion-extension views), MRIs, CT scans, oblique view radiographs, bone mineral density scans, and bone scintigrams. Previous treatments included facet blocks, epidural steroid injections, trigger point injections; transcutaneous electrical nerve stimulation; spinal cord stimulation; physical therapy; and trials of opioid agents, antidepressants, nonsteroidal anti-inflammatory medications, and anti-epileptic drugs. Six (24%) had back surgery. Table 1 lists other patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Scoliosis</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Diffuse, degenerative vertebral disease</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Low bone mineral density on DEXA scan</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Listhesis</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Leg pain</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Failed back surgery</td>
<td>6 (24)</td>
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Changes in Pain Intensity

Data on changes in pain intensity are limited to the 23 of the 25 patients who had a baseline pain rating prior to treatment, as well as pain rating assessments approximately three weeks after each pamidronate treatment. The median interval between the baseline pain rating and the final rating upon which our analyses are based was 77 days (interquartile range: 63–275 days). Twenty patients completed the series of three infusions, two had two infusions, and one had one infusion. The patient who stopped after the first infusion could not tolerate the flu-like symptoms experienced during the three days after the infusion, and the other two patients stopped because they did not have pain relief.

Compared to pre-treatment NRS pain scores, post-treatment scores were lower in 21 (91%) patients. The mean pain change was a decrease of 3.6 points (SD: 2.5; $P < 0.0001$), and the mean percentage change was decrease of 41% (SD: 29%; $P < 0.0001$). In 18 (78%) patients, the absolute reduction in the NRS pain score was greater or equal to 2.0 points, and in 13 (57%) patients, the percentage reduction in the NRS pain score was greater or equal to 30%. When we excluded the 7 patients whose interval between the baseline and final pain ratings was greater than 3.5 months, the results were similar; that is, the mean pain change was a decrease of 3.4 points (SD: 2.7; $P < 0.0002$). We found no significant relationship of percentage pain changes to age, ethnicity, or sex (however, of the 23 subjects, only 4 were men).

Changes in Use of Analgesic Medications

Among the patients not taking analgesics (nonopioids) before pamidronate treatment,
none were taking such medications after pamidronate treatment. Three patients who had been taking nonopioid analgesics (e.g., NSAIDs) before treatment stopped taking them by the time they had completed their pamidronate treatment. Although the correlation between changes in pain and opioid dose was small ($r = 0.1, P = 0.7$), the direction was positive; that is, those with pain reductions tended to have reduced their opioid medication.

**Side Effects**

No patient showed any signs, or complained of symptoms, that were suggestive of hypocalcemia. Follow-up post-infusion laboratory blood tests revealed no relevant changes from baseline results. We observed that 10% of the patients developed some discomfort at the intravenous site, which subsided in 1–15 days. Although 40–50% of patients develop mild diffuse body aches and transient fever after treatment (even with acetaminophen and ibuprofen), 95% choose to continue treatment with additional infusions. No nausea, vomiting, or other specific side effects were reported or noted.

**Discussion**

In interpreting our results, three major issues need to be considered. First, are the observed decreased scores in pain intensity following pamidronate treatment clinically significant? Second, in light of the open-label nature of our treatment, what can we say regarding the role of a placebo effect? Third, what are the possible mechanisms for the apparent analgesic effect of pamidronate?

**Clinical Significance**

Farrar et al. evaluated the clinical importance of chronic pain intensity changes measured on a 0–10-point NRS by comparing those changes to “patient global impression changes” (PGIC) for 2724 patients from 10 recently completed placebo-controlled trials. Of those, 659 patients had participated in analgesic trials for chronic low back pain. PGIC categories of “much improved” and “very much improved” were used as determinants of clinically important differences. The authors found that an absolute difference of 2 points in the numeric pain rating scale, or a score reduction of approximately 30% of the baseline numeric rating, represented a clinically important difference. These findings are similar to those regarding the efficacy evaluation of treatment of cancer-related breakthrough pain (where adequate relief was defined by the patient’s decision not to use another dose of opioid medication as a rescue in addition to the study medication used for each painful episode), as well as to findings regarding post-stroke pain, pain in diabetic neuropathy, and acute post-operative pain. Thus, both the absolute differences in pain intensity scores, as well as the percentage of pain changes, indicate that our patients experienced clinically significant pain reduction.

**Placebo Effect?**

Although we cannot determine how much of the pain improvement is attributable to a placebo effect, we may ask how our improvement rates compare to published placebo rates. In two controlled studies of intravenous bisphosphonates, one for complex regional pain syndrome, the other for cancer bone pain, respectively, 24% and 32% of the patients in each placebo study group reported some improvement in pain. Although these data come from studies in cancer pain and complex regional pain syndrome, they suggest that in bisphosphonate-treatable conditions, up to 30–35% of patients may experience a placebo effect. This is consistent with the magnitude of the placebo effects that Turner et al. reported specifically for spinal pain (20–40%).

In considering our findings, one must bear in mind that they are based on a review of medical records, and therefore intervals between baseline and final pain scores varied. Nevertheless, it is noteworthy that: a) almost all patients reported less pain after treatment, and, in fact, the proportion with less pain was much greater than published placebo effects for comparable situations; b) the vast majority reported what would be considered clinically significant pain relief; and c) the mean pain relief for the 16 patients whose interval between pain reports was less than 3.5 months remained almost the same when we included patients who had longer intervals between reports.

On balance, however, we should bear in mind the warning of Turner et al. in the absence of
independently evaluated randomized controlled trials, the true causes of improvements in pain after treatment remain unknown.

Possible Mechanisms

Possible mechanisms for pamidronate’s analgesic effect may be related to the drug’s inhibition of the osteoclast process and its anti-inflammatory effect.\textsuperscript{17,19} Inflammatory substances associated with tumor-related osteolysis include tumor necrosis factor (TNF), interleukin-1, epidermal growth factor (EGF), transforming growth factor (TGF) alpha and beta, and platelet derived growth factor (PDGF). In vitro and in vivo studies show that certain bisphosphonates inhibit the synthesis of pro-inflammatory cytokines; for example, interleukin-1, interleukin-6, and TNF-\textgreek{a}.\textsuperscript{12,27} TNF-\textgreek{a} and other proinflammatory interleukins may play a key role in the mechanism of cancer as well noncancer related pain, in particular in forms of intractable nociceptive (i.e., resistant to nonsteroidal inflammatory drugs) and neuropathic inflammatory pain.\textsuperscript{20-34}

Conclusions

Intravenous pamidronate therapy may be a promising treatment intervention in the management of chronic spinal pain. A definitive, double-blind, placebo-controlled, randomized clinical trial is warranted to confirm the apparent benefit of pamidronate for debilitating, chronic, spinal pain.

Acknowledgments

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References


