Orbital Inflammatory Disease After Pamidronate Treatment for Metastatic Prostate Cancer

Pamidronate sodium is a bisphosphonate drug used to inhibit bone reabsorption in the treatment of the hypercalcemia of malignancy, Paget disease of bone, and osteolytic bone metastases. It is administered as a slow intravenous infusion and is excreted renally. Although its mechanism of action is incompletely understood, it inhibits osteoclastic activity in vitro and binds directly to hydroxyapatite within the bone matrix.

The most common adverse effects of pamidronate infusion are nausea and anorexia. Ocular adverse effects are rare but include conjunctivitis, anterior uveitis, episcleritis, and scleritis. One case of orbital inflammation occurring 6 days after pamidronate treatment has been reported. Most of these patients had Paget disease of bone, which generally requires higher and more frequent doses of the drug.

We describe 2 patients who developed orbital inflammation after treatment with pamidronate for bone-involving metastases and discuss the implications both for the drug’s mechanism of action and for the pathogenesis of this disease.

Report of Cases. Case 1. A 63-year-old man was diagnosed as having advanced prostate cancer in November 1997. Bone metastases were found in the thoracic spine and ribs, and the patient underwent external beam radiotherapy. In October 1999, 6 days after receiving his first infusion of pamidronate, he had a sudden onset of left orbital pain and then developed diplopia with upgaze. At examination, his corrected visual acuity was 20/20 OU. Confrontational visual field measurements were full to finger counting. Pupils were equal and round without a relative afferent pupillary defect. Posis and proptosis were absent. Elevation of the left eye was mildly restricted, and a 3-prism dioptric left hypotropia was measured in upgaze. Upper and lower eyelid edema, conjunctival injection, and mild chemosis were present in the left eye. No anterior segment or vitreous inflammation was observed. The results of a dilated fundus examination were normal. Magnetic resonance imaging of the brain and orbits with gadolinium contrast showed no evidence of a metastatic lesion. The patient was treated with oral prednisone (80 mg/d), experienced prompt resolution of his symptoms, and received no further doses of pamidronate.

Case 2. A 64-year-old man was treated for prostate cancer with a radical prostatectomy in 1991 followed by treatment with leuproside acetate and flutamide. In the spring of 2002, he was diagnosed as having osteopenia and received his first infusion of pamidronate in July 2002. Within 24 hours, he experienced lower extremity myalgia and arthralgia. The next day he noted retrobulbar pain, initially in the left eye but progressing to involve the right eye. He then developed bilateral periorbital swelling. A clinical diagnosis of orbital inflammation was made, and computed tomography of the orbits with iodinated contrast revealed no gross abnormalities. Oral prednisone (80 mg/d) was prescribed, and the symptoms rapidly abated. The patient was seen at a referral visit 3 weeks later, by which time his prednisone dose had been tapered to 30 mg/d. He was pain free, and his examination results were normal. Review of his computed tomographic scan results confirmed the absence of mass orbital lesions. The patient was instructed to continue his prednisone taper and forego further treatment with pamidronate.

Comment. In early clinical trials of pamidronate and in postmarketing reviews, ocular adverse effects including conjunctivitis, anterior uveitis, episcleritis, and scleritis were infrequently noted within 1 to 6 days of administration. Orbital inflammation has been reported in a patient who received pamidronate 24 hours previously for Paget disease of bone. In this case, initial antibiotic therapy for presumed infectious orbital cellulitis produced no response, and significant visual deterioration ensued. Subsequent use of systemic corticosteroids allowed a prompt and complete recovery.

Animal studies performed prior to human clinical trials showed ocular adverse effects including conjunctivitis and episcleral congestion in rabbits after daily intravenous treatment for 6 months with 30 mg/kg of pamidronate sodium, a dose more than 100-fold greater than that used therapeutically. The symptoms remitted if treatment was withheld for several weeks or if the dose was reduced by 75%. There are no reports of posterior segment or orbital inflammatory disease in any of the animal models studied.

Although it has been suggested that the secretion of pamidronate into tears may cause conjunctivitis, the mechanism by which inflammation affects other ocular structures remains unknown. Treatment with bisphosphonates is known to trigger the release of cytokines interleukin 1 and interleukin 6 along with other acute-phase proteins. No specific localization of these factors to the eye or orbit has been reported. A few patients in previous case reports of ocular inflammatory disease had transient fever prior to the onset of symptoms, but most affected patients did not. In patients with Paget disease of bone, palliative pamidronate treatment is given for longer periods at higher doses and may heighten sensitivity to the drug. It has been proposed that patients with other diseases, particularly malignancies, are less likely to develop autoimmune-related adverse effects owing to a general down-regulation of cytokine production. Harboring a malignancy is considered a relatively immunocompromised state, which might be protective for ocular inflammatory disease. Both of our pa-
tients had metastatic prostate cancer with bony lesions amenable to pamidronate treatment. Neither had a history of ocular or connective tissue disease.

The close temporal relationship between pamidronate infusion and the onset of orbital symptoms in our patients is in agreement with prior reports of pamidronate-related ocular and orbital inflammation.\(^1\)\(^-\)\(^3\) Rapid response to pamidronate withdrawal and prednisone therapy supports a drug-related etiology for this orbital process. These 2 cases represent a potentially serious adverse effect of pamidronate that has not been noted previously in the treatment of malignancy. Whether this process represents a distinct pathogenic entity or is rather an orbital equivalent of previously described anterior segment inflammation remains to be determined.

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**Improved Technique for Temporary Tarsorrhaphy With a New Cyanoacrylate Gel**

The use of cyanoacrylate adhesive to form a temporary tarsorrhaphy was first reported by Schimke and Ballou in 1966. They applied Eastman 910 monomer (methyl 2-cyanoacrylate), a clear, colorless liquid adhesive, to the upper eyelashes of 4 patients via a cotton-tipped applicator or the metal spear from the tube and approximated the eyelashes to the skin of the lower eyelid. Numerous reports have discussed accidental tarsorrhaphy of the eyelids and eyelashes from accidental splashing of acrylic adhesive into the eye.\(^4\)\(^-\)\(^5\) Other studies have shown the efficacy of using either fibrin glue or cyanoacrylate glue to close corneal perforations up to 3 mm in diameter.\(^5\)\(^-\)\(^6\) In 1991, Donnenfeld et al\(^6\) discussed the technique of applying liquid cyanoacrylate with an applicator tip to the upper and lower eyelashes to form a temporary tarsorrhaphy in patients who are unsuitable for more invasive or permanent procedures. We report that the use of the new gel form of cyanoacrylate facilitates the application process, affords better control of tarsorrhaphy length, diminishes any secondary abrasions from applying the liquid adhesive from the standard tube, and reduces the possibility that the glue will spill over the eyelid margin and solidify in the fornix.

**Report of a Case.** An 81-year-old black woman sought treatment at our eye clinic for left eye pain. She was currently admitted to the hospital for a cardiac workup secondary to chest pain. Her medical history was significant for hypertension, diabetes mellitus, atrial fibrillation, and glaucoma. She was being treated with warfarin sodium, heparin, oral hypoglycemics, and atenolol. Her ocular history revealed glaucoma, bilateral cataract extraction with implants, and a left corneal transplantation, although the patient did not remember exactly when any of the procedures had been performed.

Visual acuity was 20/40 OD and 20/400 OS at 14 inches without correction. Her pupils were unresponsive secondary to prior surgery. She demonstrated full ocular motility and intraocular pressure of 10 mm Hg OD and 17 mm Hg OS with Schiotz tonometry. Findings from an external lid examination were normal. Her left conjunctiva was slightly hyperemic. The left cornea contained a mildly edematous corneal graft with an epithelial defect in the inferolateral quadrant measuring approximately 2 mm in diameter. There was no anterior chamber reaction. A dilated fundus examination revealed a cup-disc ratio of 0.95% in the right eye but no view of the left fundus. B-scan ultrasonography of the left eye revealed only a posterior vitreous detachment. The patient was prescribed antibiotic prophylaxis for the epithelial defect, frequent corneal lubrication, and a topical glaucoma medication. Over the next 2 days the defect did not heal, so we decided to create a temporary tarsorrhaphy. Because of the patient's hypocoagulable state, we ruled out an invasive tarsorrhaphy procedure.

After informed consent was obtained, sterile cyanoacrylate liquid was applied to the lateral eyelid margins using an applicator tip. This immediately ran over the eyelid margins onto the conjunctiva and extended too far medially onto the eyelids. Most of this material had to be removed because it was noted to have jagged edges as it hardened within the inferior fornix and would have caused further corneal injury if left in place. We then decided to try the new gel form of cyanoacrylate. The cyanoacrylate gel was applied, with an easily controlled amount, to the eyelid margin and eyelashes. The standard applicator tip, supplied with the gel, was used, and we did not need additional tips, syringes, or needles. Owing to the gel's quick hardening and ability to stay in the location in which it was applied, the lateral eyelids now stayed well approximated once closed with the gel, without any escape of the gel medially onto the eyelid margins or posteriorly into the fornix.

The gel is manufactured by Pacer Technology (Rancho Cucamonga, Calif). It is composed of ethyl-2-cyanoacrylate, polyethylene-methacrylate, and hydroquinone (0%-1%). The gel has a specific gravity of 1.05 and is polymerized by water, alcohol, amines, alkaline materials, and direct UV exposure.

**Comment.** The use of cyanoacrylate is an excellent method for cre-