

Original Article

Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability

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Abstract. Pamidronate (aminohydroxypropylidene bisphosphonate, APD) is an effective agent for treatment of Paget's disease of bone, and it has also been thought to be effective for treatment of osteoporosis. We desired to study a newer, time-release preparation of pamidronate, and carried out a placebo-controlled, double-masked study of postmenopausal osteoporosis. The original formulation was in a rapidly dissolving gelatin capsule. We encountered four episodes of esophagitis in 49 enrolled patients. We therefore discontinued treatment with this preparation and later began the study again using a standard tablet preparation. We encountered an additional case of erosive esophagitis in 1 patient of 40 receiving this tablet preparation. No patient was receiving concomitant medication which could cause esophagitis. Two of the patients gave a past history of hiatal hernia and 1 gave a history of gastric ulcer 27 years previously. The diagnosis of esophagitis was confirmed in all cases by endoscopy. Healing of the esophagitis promptly ensued after discontinuation of the pamidronate and the use of antacid medication.

Keywords: Bisphosphonate toxicity; Esophagitis; Osteoporosis; Pamidronate

Introduction

Pamidronate (aminohydroxypropylidene bisphosphonate, APD) is effective when given intravenously for hypercalcemia of malignancy [1–5] and Paget's disease of bone [1,6] and has been used orally for treatment of osteoporosis [7–10]. The most common side-effect of the intravenous treatment is fever and nausea. The principal side-effects of oral pamidronate therapy have been dose-related nausea, vomiting, and occasionally gastritis, which have been reported in 0 to 50% of patients undergoing treatment with this drug [2–6]. In a trial of oral pamidronate for osteoporosis, we recently encountered marked erosive esophagitis in 5 patients. Since this side-effect has not been documented and because pamidronate in various formulations (enteric-coated tablets, plain tablets and solutions) has previously been widely used outside the United States, we feel it is important to describe these cases in some detail.

Subjects and Criteria

The criteria for selection of patients included fully ambulatory women age 40 years or over, and the presence of osteoporosis documented by bone mineral density of lumbar spine below the second percentile of normal for premenopausal women. Patients were excluded who had any gastrointestinal disease possibly causing malabsorption; endocrine disease such as Cushing's disease, diabetes mellitus, thyroid or parathyroid disease; or other conditions known to affect bone

metabolism. Any drug treatment known to affect bone metabolism was also cause for exclusion, but stable doses of thiazides were permitted.

Treatment

Initially we randomized 49 patients into three treatment groups: placebo capsules (16 patients), APD capsules cyclic and APD capsules continuous (33 patients). The placebo regimen provided two gelatin capsules containing inert enteric pellets, orally at bedtime, daily for 26 weeks. The cyclic regimen provided two gelatin capsules, each containing enteric-coated pellets of 75 mg APD, orally at bedtime, daily for 28 days, followed by two APD capsules given once per week for 22 weeks, placebo capsules being given each of the other 6 days of the week. The continuous regimen provided two capsules (150 mg) APD orally at bedtime daily for 26 weeks. Each patient was given 1000 mg daily of supplemental calcium carbonate (Os-Cal 500, twice daily). Forty-nine patients entered the study in September 1990: 37 at the Mayo Clinic, Rochester, Minnesota, and 12 at the Mayo Clinic, Scottsdale, Arizona. The development of esophagitis in 4 patients, however, forced us to interrupt the study after 4 months. No symptoms occurred in patients receiving placebo.

We postulated that the capsule preparation could be causing esophagitis because of prematurely dissolving in the esophagus, despite our instructions to drink copious amounts of water while standing, and designed a similar trial using the tablet preparation of APD widely used in Europe, South America and Canada. Into this second phase of the study we entered 46 patients (15 placebo and 31 drug-treated) of whom 13 had previously received placebo, and 33 newly recruited patients. This phase began in March 1991, and patients were again randomized into three groups: placebo tablets, APD tablets cyclic and APD tablets continuous. Each APD tablet contained 150 mg APD. The cyclic regimen provided one APD tablet daily on rising for 28 days, followed by one APD tablet once per week for 22 weeks, a placebo tablet being given on the other 6 days of the week. The continuous regimen gave one APD

tablet daily for 26 weeks. All patients again received 1000 mg daily of supplemental calcium carbonate.

Results

The clinical characteristics of the subjects are shown in Table 1. Four of 33 patients receiving gelatin capsules of APD developed symptoms of severe epigastric pain, dysphagia, vomiting and (in 1 patient) weight loss, beginning after 2 days of treatment in 1 patient, 3 days in 1 patient, 7 days in 1 patient and 45 days in 1 patient. (Two of the patient's were under study at Mayo Clinic Rochester and 2 at Mayo Clinic Scottsdale). Upper endoscopy was carried out in each patient and confirmed the diagnosis of erosive esophagitis in each case. All 4 patients had received the APD capsules continuously.

One of the 16 patients receiving tablets of APD continuously also developed symptoms of epigastric distress after 7 days of treatment. She stopped treat-

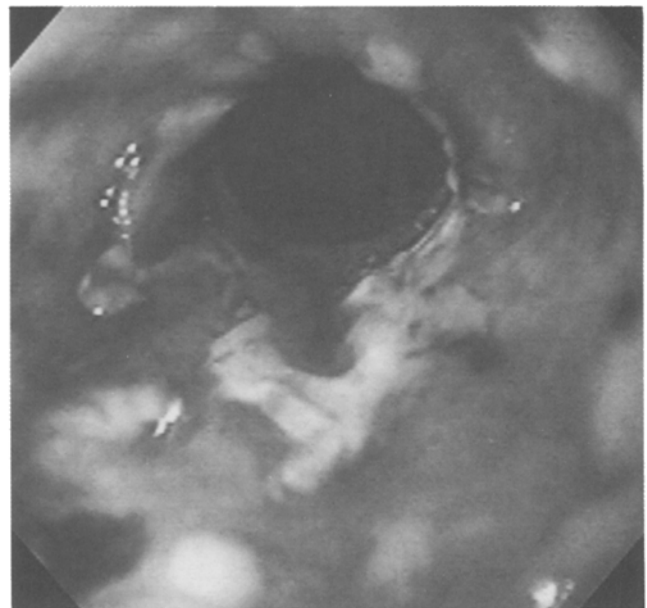


Fig. 1. Endoscopic view of erosive esophagitis in patient 2, showing multiple discrete ulcerations and pseudomembrane formation.

Table 1. Clinical characteristics of study patients with esophagitis

Patient:	1	2	3	4	5
Age (yr):	64	67	73	69	74
History of GI disease:	0	0	Hiatal hernia	Hiatal hernia	?History of gastric ulcer 27 years ago
Other oral drugs in past year:	Ibuprofen, glucocorticoids (10 months before)	Chlorothiazide, conjugated estrogen, nicotinic acid	Calcium carbonate	Meclizine, HCl	Acetaminophen 1-2/week
Endoscopy:	+	+	+	+	+
Duration of APD treatment:	4 days	4 days	7-10 days	45 days	17 days (melena day 25)
Course:	Complete healing by endoscopy 6 weeks after drug stopped	Complete cessation of symptoms	Complete recovery	Rapid recovery	Asymptomatic in 3 days

ment 4 days later. Seven days later endoscopy revealed esophagitis.

The endoscopic features are illustrated in Fig. 1 and were similar in each case. The pathology was limited to the distal esophagus; the stomach and duodenum were relatively spared. Linear erosive and exudative esophagitis without clear ulcer formation was regularly encountered, and focal gastritis was also noted in 2 cases. Fortunately, symptoms responded within 5 days to discontinuation of the study drug and to the administration of therapy (as summarized in Table 1). Healing was confirmed endoscopically in 1 case, but endoscopy was not repeated in the other 4 cases.

Discussion

The occurrence of mild gastrointestinal side-effects in up to 50% of patients taking oral APD suggests that the drug may be toxic to mucous membranes in some patients. However, erosive esophagitis has never been reported. Since APD is the most widely prescribed bisphosphonate after etidronate, we suspect that esophagitis may be occurring more often than now apparent.

Harinck et al. [6] stated that oral APD could cause esophagitis if treatment was not discontinued. However, it seems likely that the gelatin capsule used in our study in some way rendered the patients more susceptible to this complication than other preparations of the drug (enteric-coated tablets, solutions, etc.). It may also be that the presence of hiatal hernia renders a patient more susceptible to this complication [11]. However, only 2 patients of our 5 were found to have hiatal hernia by endoscopy.

The pattern of esophagitis noted in our patients by endoscopy is typical for drug-induced esophagitis which ordinarily involves the middle or distal segments of the esophagus: it shows a clear time and dose correlation with the administered drug and causes multiple discrete ulcers, often associated with hiatal hernia [12]. Our patients were carefully screened by general medical examination and were felt to be healthy except for their osteoporosis upon admission to the study. After our initial case of esophagitis, all patients had been instructed to follow procedures known to facilitate passage of tablets through the esophagus: to take the medication on an empty stomach with 8 ounces (225 ml) of water and not to recline for 1 hour [9]. We postulate that the capsules may have adhered to the distal esophagus, dissolving the gelatin coating, and thus, because of increased esophageal pH in these patients, the enteric coating of the pellets dissolved, causing direct irritation of the esophageal mucosa by the bisphosphonate. Alternatively, the capsules may have dissolved in the stomach, and the pellets could have been refluxed back into the distal esophagus due to a recumbent position.

The side-effects of intravenous APD (transient fever in 27%, nausea in 18%, transient hypocalcemia in 6%–12% and local thrombophlebitis in 18%) are quite distinct from the side-effects noted with oral APD, and give further evidence that esophagitis is caused by a direct, toxic effect of the drug as it first encounters mucous membranes.

Although esophageal ulceration has not been reported with bisphosphonates, these drugs have caused gastrointestinal symptoms [2–6]. A review of the structure of APD [6] does not suggest unique features that would account for the esophageal side-effects that we observed. These observations raise the possibility that other bisphosphonates could cause esophagitis. Because our clinical trial ended prematurely as a result of the side-effects, we are unable to draw conclusions about APD's efficacy in preventing bone loss.

We conclude that APD can cause serious esophagitis when given either as oral gelatin capsule or as tablets. These findings may have implications for human studies of other bisphosphonates.

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