Duration of Etidronate Effect Demonstrated by Serial Bone Scintigraphy

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There have been several reports of etidronate disodium (EHDP) interference upon the biodistribution of ^{99m}Tc-methylene diphosphonate (MDP). With the increasing use of etidronate for the treatment of Paget's disease, hypercalcemia, and osteoporosis, nuclear physicians can expect to encounter increasing numbers of cases in which EHDP-induced artifacts impair the diagnostic utility of bone scans. The temporal duration of this effect is unknown yet obviously important. We report serial bone scintigraphy in a patient who received a single dose of EHDP for hypercalcemia. Normal biodistribution of ^{99m}Tc-MDP was noted at 15 days, suggesting that 2 wk are sufficient before performing a bone scan after a single intravenous dose of etidronate.

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Radionuclide bone scans are an integral part of the diagnostic evaluation of cancer patients with potential metastatic bone disease. Many pharmaceuticals, including some cancer chemotherapeutics, seem able to alter the biodistribution of ^{99m}Tc-methylene diphosphonate (MDP), producing studies that may be difficult to interpret.

Etidronate disodium (EHDP) is a diphosphonate that has been shown to be effective in the treatment of Paget's disease (*1–3*), hypercalcemia (*4–7*) and, more recently, osteoporosis (*8*). An effect of EHDP on the biodistribution of ^{99m}Tc-MDP in skeletal scintigraphy was initially demonstrated by Watt and Hill (*9*) in the rat model. What they showed was a typical carrier effect with a dose-related interference in the skeletal ^{99m}Tc-MDP uptake. This presumably results from the competition between the radioactive diphosphonate and the massively larger concentration of the non-radioactive diphosphonate. Two patients treated with EHDP who subsequently had bone scans support the animal data and suggest that the administration of EHDP may decrease the sensitivity of the bone scan for the detection of metabolic and metastatic bone disease (*10,11*).

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With the increasing use of therapeutic EHDP, especially considering its anticipated larger scale application to the common disorder osteoporosis, nuclear physicians can expect to encounter increasing numbers of cases in which EHDP-induced bone scan artifacts impair their diagnostic utility. The temporal duration of this effect is unknown and obviously important. Some have predicted that the effect may last for months, based on the 20-30-day biologic half-life of EHDP in the skeleton (*10*). To date, however, there have been no studies to determine how long the interfering effects of etidronate last. We report serial bone scan findings in a patient with EHDP-treated hypercalcemia.

CASE REPORT

Clinical History

A 69-yr-old man presented with muscle weakness and 3 mo of increasing abdominal pain. His medications included acetazolamide, triazolam, doxepin, ipratropium bromide, metaproterenol sulfate, theophylline, and beclomethasone. He had a history of peptic ulcer disease and had recently increased his intake of a proprietary calcium carbonate antacid to treat his dyspepsia.

On admission, physical examination revealed T36.^{2}, P90, RR20, and BP 152/88. Mental status changes including confusion and Grade 4/5 lower extremity muscle weakness were the only physical findings. Admission serum calcium was 15.8 mg/dl; which 2 mo prior had been 10.0 mg/dl. The patient was treated with intravenous hydration, furosimide, and a single intravenous dose of 450 mg of etidronate.

An extensive diagnostic work-up, including 1,25-dihydroxyvitamin D3, and PTH levels, serum and urine electrophoresis, CXR, head CT, renal and transrectal ultrasound, bone scan, colonoscopy, cystoscopy, and prostate biopsy, made malignancy unlikely. The hypercalcemia was ultimately attributed to milk-alkali syndrome.

The milk-alkali syndrome, first described in 1915 (*12*) in patients with peptic ulcer disease, occurs in persons ingesting large quantities of calcium products and absorbable alkali (*12–15*). The major findings include hypercalcemia, alkalosis, and renal impairment.

Bone Scan Findings

The first bone scan was obtained within 24 hr of an intravenous administration of a single dose of 450 mg of etidronate. The scan revealed a dramatic and unexpected decrease in bone uptake with

FIGURE 1. Bone scan performed within 24 hr after administration of a single dose of 450 mg of etidronate. A dramatic decrease in bone uptake along with prominent renal parenchymal activity is seen. Traumatic rib lesions are faintly seen along the left costochondral junctions. Increased soft-tissue retention is evident.

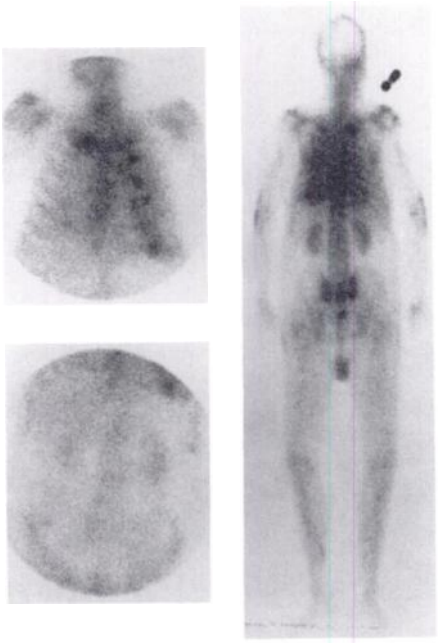

FIGURE 2. Repeat bone scan, 4 days after the first, shows persistence in impaired bone uptake with some improvement in the spine, ribs, and pelvis. The lung parenchyma shows MDP activity consistent with metastatic calcification due to hypercalcemia. The kidneys show less intense uptake due to either partial resolution of the etidronate effect or to an improvement in the patient's hypercalcemic status.

considerable soft-tissue uptake. The kidneys were well visualized and activity was noted in the bladder. Focal abnormalities were seen in the costochondral junctions on the left, consistent with the patient's history of trauma to this region from a recent fall, and pulmonary localization from metastatic calcification was present (Fig. 1).

Routine quality control testing of the radiopharmaceutical used revealed excellent tagging efficiency and no aluminum breakthrough. Additionally, other bone scans performed that day with the same preparation of ^{99m}Tc-MDP were of diagnostic quality.

Four days later, after EHDP was discontinued, the bone scan was repeated and showed persistence in impaired bone uptake (Fig. 2). The third bone scan, performed 15 days from the first, demonstrated normal biodistribution of the radiopharmaceutical (Fig. 3). This suggests that approximately 2 wk are sufficient before performing a bone scan after a single intravenous dose of etidronate.

DISCUSSION

EHDP is used to treat hypercalcemia (*4–7*), Paget's disease (*1–3*), and osteoporosis (*8*). Disodium etidronate (ethane-1-hydroxy-1-diphosphonate, Didronel) is a substituted diphosphonate that has been used in radionuclide bone imaging when labeled with ^{99m}Tc. Development of this agent followed the use of ^{99m}Tc-pyrophosphate substituting the P-O-P bonds of pyrophosphate with P-C-P bonds (*16*). The diphosphonates are less bound to plasma proteins and clear more rapidly from the blood. Pyrophosphate has been shown to inhibit the formation and dissolution of hydroxyapatite crystals and prevent the development of ectopic calcification (*16–18*). The diphosphonates have a similar mechanism of action. This has led to their use in retarding ectopic calcification in children with myositis ossificans progressiva (*19*) and in reducing serum alkaline phosphatase and urinary hydoxyproline in active Paget's disease.

In a study by Kanis et al. (*5*), short courses of diphosphonates given to patients with Paget's disease were found to suppress bone turnover for months to years after with-

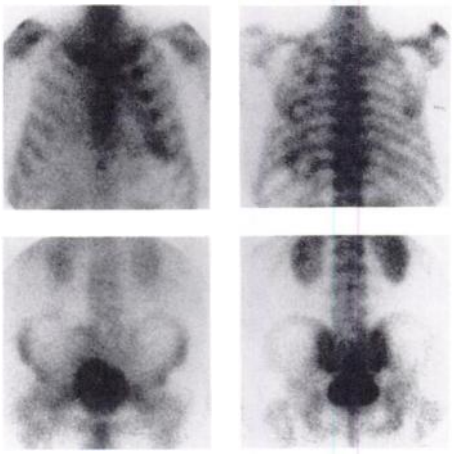

FIGURE 3. Repeat bone scan, 15 days after the first, demonstrating normal biodistribution of the radiolabel. Also, note the increase in urinary excretion compared to Figures 1 and 2.

drawal of treatment. The mechanism of this prolonged effect is not known, but it is of interest considering that our patient showed little residual effect due to etidronate on his bone scan by two weeks.

The effects of EHDP on the distribution of ^{99m}Tc-labeled MDP was studied by Watt et al. (*9*) in the rat. Extensive changes in bone, kidney, and blood levels of the bone agent were observed. They showed that carrier EHDP resulted in a poor quality image from the decreased bone/blood ratio and suggested that this might lead to a false impression of disease resolution. In a study by Goldman et al. (*3*), the therapeutic efficacy of EHDP in the treatment of Paget's disease was studied using bone scans. Decreased tracer uptake was interpreted as clinical improvement. Although these changes correlated with clinical, biochemical, and skeletal x-ray improvement, the changes in radioisotopic uptake may have been due primarily to the altered biodistribution as described by Wall et al. (*9*).

Most of the studies on the efficacy of etidronate for hypercalcemia have focused on that due to malignancy. No evidence of malignancy could be found in our patient despite an extensive work-up. His response to hydration and the single dose of etidronate, as well as the lack of recurrent hypercalcemia in the weeks following discharge, have supported the conclusion that his hypercalcemia was secondary to milk-alkali syndrome.

CONCLUSION

Our patient's findings address the duration of effect of EHDP on bone scintigraphy and demonstrate that despite the reported extended time course of pharmacologic effect the influence of etidronate on the biodistribution of MDP appears to be much shorter. The mechanism may well be due to competition of ^{99m}Tc-MDP with EHDP which is not radiolabeled—a carrier effect. In our series of three bone scans performed in a patient who received a single dose of EHDP intravenously, we found that a very adequate bone scan could be obtained at 2 wk. What the time course would be in patients on chronic EHDP therapy is of interest and is probably longer. This would be influenced by the amount of drug accumulated and should be studied.

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