The Bisphosphonate Dilemma

TO THE EDITOR: We read with interest the article by Pecherstorfer et al. as to the effect of bisphosphonate (diphosphonate) treatment on bone scintigraphy (*1*). Because of their potency and duration of action, bisphosphonates are considered to be best when life is threatened with intractable hypercalcemia. Humoral hypercalcemia of malignancy is the most common cause of severe hypercalcemia associated with bone metastases. Radionuclide bone scintigraphy with ^{99m}Tc-hydromethylene diphosphonate (HMDP) or methylene diphosphonate (MDP) is a routine procedure to evaluate patients with metastatic carcinoma in the bone. There is conflicting data, however, as to whether previous bisphosphonate treatment for metastatic bone disease might give rise to false-negative bone scans. Pecherstorfer et al. concluded that intravenous clodronate treatment did not impair the sensitivity of ^{99m}Tc-MDP bone scintigraphy in detecting bone lesions in patients with metastatic breast cancer (*1*). On the other hand, several authors have suggested that the clinician may have to wait for an interval (i.e., two or more months) after discontinuing bisphosphonates to perform bone scintigraphy (*2–4*). It is almost impossible to discontinue the drugs for even a week in the case of life-threatening hypercalcemia patients.

We recently reported on a 62-yr-old woman with hypercalcemia due to bone metastatic parathyroid carcinoma (*5*). The patient had received a single intravenous infusion of alendronate (10 mg) on the day before scanning with ^{99m}Tc-HMDP. Bone scintigraphy failed to reveal lesions. Although we were aware of the possibility of competitive interaction between alendronate and radiolabeled bisphosphonate, we could not discontinue the bisphosphonate to restudy the bone scintigraph because of severe hypercalcemia. Thus, medical management with bisphosphonates poses a dilemma. Divergences among case reports might be attributed to variant pharmacokinetic characteristics of the bisphoshonates used [clodronate (*1*), etidronate (*2–4*) and alendronate (Koyano H, et al., unpublished results)] or carcinoma characteristics [breast cancer (*1,3*), prostate cancer (*2*) and parathyroid carcinoma (*4*)]. For example, alendronate can specifically inhibit the accession of osteoclast precursors to mineralized matrix, but clodronate cannot in vitro (*5*). The study by Pecherstorfer et al. is the first well-designed one, but further clinical studies are required in order to overcome such a dilemma.

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REPLY: Koyano et al. found impaired radionuclide imaging of bone metastases following intravenous treatment with 10 mg of the bisphosphonate alendronate (*1*). This report does not, in fact, contradict our experiences that the sensitivity of bone scintigraphy was not reduced by intravenous bisphosphonate therapy administered daily for 21 days up to 24 hr prior to the bone scan (*2*). In our investigation, only breast cancer patients with normal or slightly elevated serum calcium (<2.65 mmole/liter) were included. Moreover, predominantly osteolytic bone metastases were an exclusion criterion, since radionuclide imaging of bone lesions depends upon a local osteoblastic reaction (*3*). In contrast, Koyano et al. treated a patient with parathyroid carcinoma and hypercalcemia. Unfortunately, the radiological appearance of the bone metastases (sclerotic, mixed or osteolytic) is not mentioned. Koyano et al. also stated that the patient had severe hypercalcemia (as is usual in parathyroid cancer (*4*)). Due to the 24-hr delay in the onset of the hypocalcemic effects of bisphosphonates, the patient obviously had raised serum calcium levels when ^{99m}Tc-HMDP was administered for bone imaging. As we discussed in our paper, formation of complexes between the labeled bisphosphonate and the calcium ions might occur in the blood of hypercalcemic patients, leading to an impaired distribution of the radiotracer (*2*).

Alendronate is a new, very potent inhibitor of osteoclast activity. With doses of alendronate as low as 5 mg, response rates comparable to the intravenous administration of 1500 mg clodronate have been achieved in the treatment of tumor-associated hypercalcemia (*5*). In our study, each patient received a cumulative dose of 6300 mg clodronate. Even if only 25 % (1545 mg) of the clodronate administered were chemisorbed to the bone (*6*), and assuming that alendronate was administered at a dose of 10 mg and completely bound to bone surface, the amount of clodronate on the osseous surface would exceed the amount of alendronate by a factor of 150. Thus, we believe that the risk of false-negative bone scans due to the saturation of the bone surface with bisphosphonates is negligible in patients treated with the new highly active bisphosphonates such as alendronate.

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