

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characteristics of the bisphosphonates used [clodronate (1), etidronate (2-4) and alendronate (Koyano H, et al., unpublished results)] or carcinoma characteristics [breast cancer (1,3), prostate cancer (2) and parathyroid carcinoma (4)].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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Radiochemical Purity of Technetium-99m-HMPAO Depends on Specific Activity

TO THE EDITOR: Radiochemical purity (RCP) quality control is routinely carried out before administering ^{99m}Tc-HMPAO. After following kit instructions for labeling (1), we observed a low RCP related to the use of pertechnetate eluates obtained approximately 24 hr after the previous elution (generator in-growth 24 hr). We suspected that the technetium used was not of sufficient quality due to radiolysis or an excess of ⁹⁹Tc (i.e., low-specific activity ^{99m}Tc), so we decided to use only the second eluates obtained within 1-4 hr after the previous elution (generator in-growth 1-4 hr).

Quality control of RCP was carried out using the method of extraction with chloroform by Ballinger (2). The correlation obtained from a study carried out previously in our laboratory when this method was compared with the chromatographic method of Neirinkx (3) was:

$$y \text{ (Chromatographic Method)} = 0.909 \times \text{(Extraction Method)} + 6.36, \quad \text{Eq. 1}$$

where $r = 0.986$, $p < 10^{-6}$, and $n = 27$.

Labeling carried out with technetium obtained with a generator in-growth 24 hr (22.6 ± 2.6) gave:

$$\text{RCP} = 85.2\% \pm 16.4\% \text{ (n = 42)}. \quad \text{Eq. 2}$$

In 15 preparations, the RCP was <90% and in 10 preparations <80% (Table 1). The results were analyzed for the effect of total amount of radioactivity. No statistical significant difference in RCP was found between both groups.

Labeling with technetium obtained with a generator in-growth 1-4 hr (2.5 ± 0.7) gave:

$$\text{RCP} = 93.9\% \pm 1.6\% \text{ (n = 181)}. \quad \text{Eq. 3}$$

Only one preparation resulted in a RCP <90%. Table 2 shows various preparations according to the radioactivity used for labeling.

TABLE 1
RCP for Two Pertechnetate Eluates

Activity (MBq)	Generator in-growth (hr)	RCP %	n
1067 ± 159	23.9 ± 2.1	83.3 ± 18.4	22
2723 ± 533	22.6 ± 2.5	87.3 ± 13.7	20

TABLE 2
Various Pertechnetate Preparations

Activity (MBq)	RCP %	n
1591 ± 222	92.0% ± 1.4	5
2216 ± 44	93.6% ± 1.5	94
2941 ± 78	94.3% ± 1.4	77
3626 ± 148	94.0% ± 1.8	5

To obtain high RCP with ^{99m}Tc-HMPAO, an elution obtained a few hours after the previous elution (within 1-4 hr) should be used. This permits an increase of radioactivity labeling to at least 3000 MBq. Furthermore, this would represent a considerable economic saving since it would result in several doses from a single vial.

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Renal Clearance of Technetium-99m-MAG3: Normal Values

TO THE EDITOR: We are frequently asked about normal values for ^{99m}Tc-MAG3 clearance. Technetium-99m-MAG3 has become the renal agent of choice in many clinical contexts. Its clearance, easily calculated from a single timed blood sample, can be used directly as a measure of renal function and can also be converted to effective renal plasma flow (ERPF) by applying a correction factor (1).

When ^{99m}Tc-MAG3 clearance (C_{MAG3}) is converted to ERPF (or C_{PAH}), conventional normal values for ERPF can be employed, such as the normal values obtained at this center from OIH clearance (C_{OIH}) in a series of normal transplant donors (2). Since renal donors have such extensive presurgical evaluation, they constitute a normal reference population in which renal disease has been truly ruled out.

We now have accumulated enough experience with ^{99m}Tc-MAG3 in transplant donors to report normal values measured directly with ^{99m}Tc-MAG3 rather than with OIH. Data from 200 donors were reviewed (86 male, 114 female, ranging in age from 20 to 66 yr). C_{MAG3} was calculated from a single 45-min blood sample by two methods (3-5) and ERPF was estimated by a third method (6). Normal values are reported for each method.

At our clinic, ERPF has been measured routinely for many years with the Tauxe one-sample method using ¹³¹I-OIH. The Tauxe ERPF formula yields values about 10% higher than true C_{OIH} (1), compensating for the difference between C_{OIH} and C_{PAH} (7). When we switched from OIH to ^{99m}Tc-MAG3, we