Evaluation by Using Radionuclide Uptake of Bone in Paget’s Disease of Bone: Special Reference to Treatment with Calcitonin

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Received February 18, 1988

Bone scintigraphy using $^{99m}$Tc-MDP was performed on 2 patients with Paget’s disease of bone before and after the treatment with a synthetic eel calcitonin analogue ((Asu$^{17}$)-eel calcitonin, ECT)) at a dose of 40 U per day. All pagetie lesions showed markedly the increased accumulation of the radionuclide. The uptake ratio, defined as the count rate of $^{99m}$Tc-MDP over each bone lesion to that over the control bone, was calculated. The response to the calcitonin therapy was evaluated with the uptake ratio of the radionuclide. The uptake ratio decreased markedly within the first 3 months of the treatment, in association with a palliation of bone pain, while the serum alkaline phosphatase activities which had been within the normal range or slightly high before the treatment did not show any significant change or did not reflect a clinical feature (e.g., bone pain) with the treatment. Thus, the uptake ratio on the bone scintigram seemed to offer the most sensitive and most reliable information for the evaluation of calcitonin treatment of Paget’s disease of bone.

Key Words: uptake ratio, Paget’s disease of bone, technetium-99m-methylene diphosphonate, calcitonin

1. Introduction

Paget’s disease of bone is a local bone disease of the unknown cause, which was first reported by Sir James Paget in 1877). In this clinical entity, the laminar bone assumes a mosaic structure through excessive bone resorption by osteoclasts and the excessive bone formation by osteoblasts, leading eventually to fibrosis of bone, characterized by an exaggerated bone metabolism in the involved bone. In the present paper 2 patients with Paget’s disease of bone were described, and the effectiveness to treatment with ECT was studied.

2. Materials and Methods

Clinical features and laboratory data in 2 patients with Paget’s disease of bone were shown in Table 1. The serum alkaline phosphatase, calcium and...
phosphorus concentrations were measured with the SMA model 12/60 analyzer. The bone X-ray was performed before and after the treatment of ECT. Bone scintigraphies were performed 3 hours after the intra-venous injection of 15 mCi of $^{99m}$Tc-methylene-diphosphonate (MDP). Spot images as well as the whole skeletal images were obtained, and on the display the region of interest (ROI) over the involved bone and the contralateral normal bone was settled, to calculate the uptake ratio of radionuclide in the 2 areas. As a treatment the ECT 40 U per day was administered every day, and its therapeutic effect was evaluated with reference to the X-ray films, bone scintigrams and blood biochemical parameters.

### 3. Results

In the lesions of the long bones, thickness of the cortical bone, coarseness of the trabecular bone, bowing of the bone, and mixed osteolysis and sclerosis are noted. According to the Greenfield classification, these 2 cases appear to be of stage 2.

The bone scintigraphies showed very high uptakes of the radionuclides in the lesions. The uptake ratios of $^{99m}$Tc-MDP on the bone scintigrams showed high values (5.5 in Case 1 and 14.0 in Case 2) before the treatment, but were significantly reduced within 4 to 5 months after the treatment. In Case 1, the treatment was stopped, as the transient facial flushes appeared 1 hour after each injection at 8 months of the treatment. As the reappearance of bone pain that had once disappeared was noted, the treatment was resumed. The uptake ratio decreased again from 5.0 to 3.5, and the bone pain disappeared after the re-treatment. Figure 1 illustrates the clinical course with ECT and EHDP treatment in Case 2, and the uptake ratio correlates well with the treatment. In Case 2, no side effects of ECT were noted throughout the entire treatment period. The concentration of serum alkaline phosphatase in Case 1 was elevated before the treatment. However, because this patient was complicated by chronic hepatitis, the elevation of this parameter seemed to be attributable to the overlapping of alkaline phosphatase of the liver origin. In Case 2, the concentration of serum alkaline phosphatase remained to be within the almost normal range during the treatment with ECT and EHDP.

### 4. Discussion

Bone scintigraphy offers clues to the correct diagnosis of Paget's disease of bone. Therefore, this is the technique of the first choice in the suspected cases. $^{99m}$Tc-MDP which showed the high accumulation in the involved bone is useful for the differentiation from other bone diseases, and also for detecting the involved lesions other than the main lesion. The increased uptake of $^{99m}$Tc-MDP is considered as representing an enhanced bone metabolism and an increased blood flow in the involved bone in this disease. The possibility of the latter was supported by the arteriograms indicative of the proliferation of blood vessels supplying the involved area and also by the blood flow scintigrams using $^{99m}$Tc-MAA. EHDP, mithramycin and calcitonin, besides anti-inflammatory agents such as indomethacin, have been exclusively used for the treatment of Paget's disease of bone. EHDP acts as being adsorbed on the surface of bone crystal to inhibit bone resorption. Mithramycin, RNA synthesis inhibitor, is effective in treating Paget's disease of bone in the relatively early stage when bone resorption is mainly occurring. Because
mithramycin has its effect of serum calcium-lowering action, it is also indicated in the cases associated with hypercalcemia or those with extensive skeletal changes. However, severe adverse reactions, e.g., immunosuppression and bone marrow depression, have been reported. Calcitonin, a binder of the membrane receptors, inhibits the activity of osteoclasts through the mediation of c-AMP. The calcitonin was initially used in the treatment of 15 cases of Paget's disease of bone in 1967, with excellent therapeutic effects. The use of calcitonin therapy with porcine, salmon and human calcitonin has since been tried, while there is few reports of the treatment with eel calcitonin. (Asu)-eel calcitonin is a synthetic analogue of natural eel calcitonin, with the S-S bond between the 1 and 7 positions of its amino acid sequence substituted for an ethylene group. Synthetic eel calcitonin has a high biological activity as 5 000 MRC units/mg, which is comparable to that of natural eel calcitonin and of natural salmon calcitonin. The therapeutic effect of calcitonin is usually evaluated with reference to changes on the bone X-ray film, and those in urinary hydroxyproline excretion, serum alkaline phosphatase, and bone pain. On the bone X-ray film, if 30 to 50% of the bone mineral is not increased or decrease, no changes are noted. Although changes in urinary hydroxyproline excretion serve as an excellent index for the bone

Fig. 1 Chronological changes of uptake ratio of Tc-MDP, serum alkaline phosphatase concentration, and bone pain in Case 2 with Paget's disease of bone, after the treatment with ECT and EHDP.
resorption, the measurement of this parameter is troublesome and time-consuming. Changes in serum alkaline phosphatase, indicative of the osteoblastic activity of the involved bone, are widely used for monitoring Paget's disease of bone. This parameter, however, is not elevated in some cases, and furthermore in the cases (Case 1) associated with liver disease, the measurement of isozyme activity is indispensable. On the other hand, as the accumulation on the bone scintigraphy is reflecting the degree of bone reaction, it has been introduced for the evaluation of therapeutic effect to this disease\(^9,10\). The uptake ratio on the bone scintigrams was reduced in association with the disappearance of bone pain after the initiation of calcitonin treatment, while the ratio was elevated during its suspension and lowered again on its resumption. Therefore, these findings might indicate that calcitonin is effective in inhibiting the increased bone reaction, and that the semi-quantification of radionuclide uptakes on the bone scintigrams is useful for the evaluation of a drug effect.

### 5. Conclusion

High accumulations of \(^{99m}\text{Tc-MDP}\) in the pagetic lesions were noted in the bone scintigrams in 2 cases with Paget's disease of bone, suggesting the existence of the activated bone reactions in the involved bones.

The treatment with a synthetic eel calcitonin was tried, and proved therapeutically effective. Furthermore, the determination of the uptake ratio of radionuclide on the bone scintigrams seemed to be useful for the evaluation of a drug effect in this disease.

### References