CASE REPORTS

Differential Skeletal Uptake of Tc-99m-Tagged Pyrophosphate and Methylene Diphosphonate in Leukemia

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Three leukemic patients showing minimal bone uptake of Tc-99m pyrophosphate but with good uptake of methylene diphosphonate are described.

J Nucl Med 24: 799–802, 1983

The radiotracers Tc-99m pyrophosphate (PPi) and Tc-99m methylene diphosphonate (MDP) have been widely used for bone scintigraphy, although MDP and its analogs have now largely replaced PPi for bone imaging. Structurally these compounds are similar, except that in MDP the P—O—P bond is replaced by a P—C—P bond. Although there are pharmacokinetic differences between the two agents, satisfactory bone scintigrams can be obtained with either (*1*,*2*).

In this paper we report three patients in whom minimal bone uptake was seen following PPi administration whereas grossly normal uptake of MDP was observed within a few days of the PPi scan.

CASE REPORTS

Case 1. A 68-yr-old white female had a poorly defined lymphoproliferative disorder with biologic behavior between chronic lymphocytic leukemia and lymphosarcoma-cell leukemia, diagnosed 3 yr before admission. She had failed to respond to several chemotherapeutic regimens. Her chief complaint was dysphagia.

On admission the patient appeared cachectic. Hepatosplenomegaly was noted on physical exam. Laboratory values included a hematocrit of 27%; WBC count 200,500/mm^3 with 93% lymphocytes, 5% polymorphonuclear leukocytes, 1% bands, and 1% monocytes; serum alkaline phosphatase 164 mU/ml (normal 30–90); calcium 9.2 and phosphorus 4.1 mg/dl. Serum iron was 194 μg/dl and total iron-binding capacity 367 μg/dl, with a saturation of 53%. Serum protein electrophoresis showed an albumin of 4.19 g/dl: α_1 globulin 0.19, α_2 globulin 0.76, and β globulin 0.95 g/dl, with IgG 1700, I_gA 265, and I_gM 170 mg/dl.

Endoscopy showed an esophageal mass that, on biopsy, was diagnosed as squamous cell carcinoma. The patient received palliative radiation therapy with improvement of her dysphagia, and was discharged to be followed in outpatient clinic.

A bone scan (Fig. 1A) with PPi,* obtained before her course of radiotherapy and before red blood cell (RBC) transfusions, showed no diagnostic bone visualization, with prominent renal and soft-tissue activity. Seven other PPi bone scans performed in our clinic the same day—including two others injected from our patient's vial—showed normal skeletal uptake. A repeat study the following day, with MDP,† (Fig. 1B) again showed increased soft-tissue and renal activity, possibly due in part to retention from the previous day, but the bony structures were satisfactorily delineated.

Review of previous studies showed two other bone scans, performed two years earlier, that also showed similarly poor bone uptake with PPi.

Case 2. A 65-yr-old white male was admitted because of melena and swelling and pain in both knees. He had acute myelocytic leukemia, diagnosed 8 mo before admission; it had given poor response to various chemotherapeutic regimens.

On physical examination, scleral icterus, sublingual hemorrhages, and hepatosplenomegaly were noted. Laboratory values included hematocrit 26%, white cell count 8,200/mm^3 with 25% immature cells, platelets 9,000/mm^3, bilirubin 5.1 mg/dl, alkaline phosphatase 380 mU/ml, calcium 9.5 mg/dl, phosphorus 2.2 mg/dl, total protein 6.8 mg/dl, and albumin 4 mg/dl.

He was treated with transfusions of platelets and packed RBCs (a total of eight units of RBCs in the 2 wk preceding the scan). Following these transfusions, his serum iron was 213 μg/dl and total iron-binding capacity 357 μg/dl with 60% saturation. He developed increasing hepatic dysfunction and died 6 wk after admission.

A PPi bone scan 3 wk before death showed very poor osseous uptake (Fig. 2A); eight bone scans from other patients performed that day, including five injected from our patient's vial, showed good skeletal uptake. A repeat study, done 5 days later because of a question of error in radiopharmaceutical administration, gave identical results. Two days later, an MDP† bone scan showed good bone visualization (Fig. 2B).

Case 3. A 63-yr-old white male was diagnosed as having acute myelocytic leukemia, and was treated with various chemothera-

Received June 8, 1981; revision accepted April 8, 1983.

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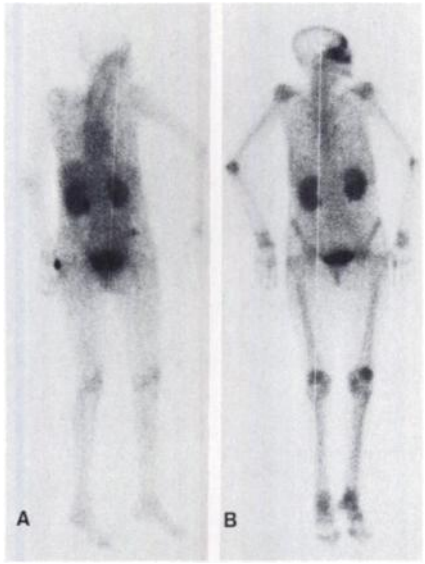

FIG. 1. Case 1 (A). PPi bone scan, anterior view. No diagnostic bone visualization. (B). Anterior MDP scan. Bilateral patellar and facial sinuses uptake can now be seen.

peutic regimens. One year later, at the time of his bone scan, his hematocrit was 34%, hemoglobin 12.3 g/dl, platelet count 22,000/mm^3, and white cell count 1700/mm^3 with 68% lymphocytes, 12% monocytes, and 4% blast forms. Serum enzymes and serum iron and iron-binding capacity were not available, but RBC transfusions had been given 1 wk before the first scan. Serum protein electrophoresis showed an albumin of 2.47 g/dl: α_1 globulin 0.37, α_2 globulin 0.75, β globulin 0.94, and γ globulin 1.67, all g/dl. Immunoelectrophoresis showed moderate increases in IgG and IgM, with no monoclonal component evident. A PPi bone scan, performed on an outpatient basis, showed minimal skeletal visualization (Fig. 3A). A second study a few days later, with MDP‡, showed a normal uptake pattern (Fig. 3B).

DISCUSSION

These findings may be explained by either a biochemical abnormality inactivating PPi in vivo, or an altered bone receptor site that allows binding of MDP but not of PPi. Unfortunately we have no data to differentiate between these two mechanisms.

There are significant biochemical differences between PPi and MDP. The P—O—P bond of PPi is readily hydrolyzed by pyrophosphatases, which exist in virtually every human tissue (*3*); a variety of enzymes possess pyrophosphatase activity, including alkaline phosphatase, acid phosphatase, several bone pyrophosphatases (*4*), and inorganic pyrophosphatase (*5*). When injected intravenously, PPi disappears rapidly from the plasma, with a turnover time of 1.3 min (*3*); for reasons incompletely understood, the Tc-99m(Sn)PPi complex injected for bone scanning is more stable in vivo. The P—C—P bond of MDP, on the other hand, is resistant to any enzyme known to exist in man (*4*). MDP is a synthetic compound not known to occur in the body, whereas PPi exists in a variety of tissues, being a product of the synthesis of many macromolecules (*4*).

Pharmacokinetic differences also exist between PPi and MDP. Bone uptake of MDP is greater than that of PPi in the rat (*6,7*) and rabbit (*1,7*). In man, PPi has a slower blood clearance than MDP, with more than twice the 3 hr blood retention (*2*), twice as much plasma-protein binding (*2*), and three to four times as much incorporation into RBCs than MDP (*1,2*). PPi had more than twice the MDP uptake in a rat myocardial infarct model (*8*), and has been shown superior to MDP as a myocardial infarct-imaging agent (*9,10*).

The mechanism of bone uptake of the Tc-labeled phosphates has not been completely elucidated. Blood flow and rate of osteogenesis are considered to be two major factors, and binding to both the organic and mineral components have been demonstrated (*11*). At the enzymatic level, local hydrolysis of pyrophosphate to inorganic orthophosphate in bone has been shown (*12*). Inhibition of acid and alkaline phosphatases by diphosphonates has been proposed as a receptor mechanism for bone uptake; this would require other substrates to stabilize the phosphatase-PPi complex (*13*).

Thus the failure of bone PPi uptake in these patients could be due to pyrophosphatase hydrolysis of PPi in the circulation, which—given the ubiquitousness of pyrophosphatases in the body—would not necessarily be reflected in a markedly elevated serum alkaline phosphatase. Alternatively, if bone uptake is enzyme-mediated, a biochemical receptor abnormality could selectively affect PPi uptake. Whether the abnormality is restricted to leukemia we cannot tell. We have performed many successful PPi scans in leukemics; conversely, we have rarely if ever observed the almost complete lack of uptake reported here in any other disease.

Some evidence for in vivo radiotracer breakdown is the presence of liver activity higher than that expected from blood-pool activity alone. Liver PPi uptake has been noted in liver necrosis (*14*) and hyperaluminemia (*15*). Since neither of these mechanisms applies to our patients, it is likely that this finding is due to radiotracer breakdown. It is known that free technetium can combine with stannous ion to form an insoluble complex that is removed by the liver (*15*).

We note that all our patients had received RBC transfusions, and in two of them transferrin saturation was mildly increased at the time of the scans (53% in Case 1 and 60% in Case 2). Iron overload has been reported to cause decreased skeletal uptake of bone-seekers (*16,17*). In all 13 patients reported, transferrin saturation levels were raised (70–97%), the impairment of skeletal uptake was less pronounced, and the effect occurred with both PPi and MDP, compared with the marked discrepancy of uptake in our cases. Thus, while we cannot exclude iron overload as a contributing factor, it seems unlikely that it alone would cause such

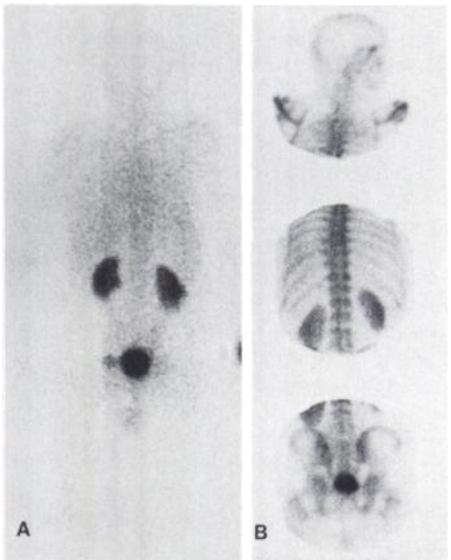

FIG. 2. Case 2 (A). Posterior PPi bone scan, obtained with gamma camera and moving table. There is minimal skeletal uptake. (B). Posterior MDP study: spot views show normal bony structures.

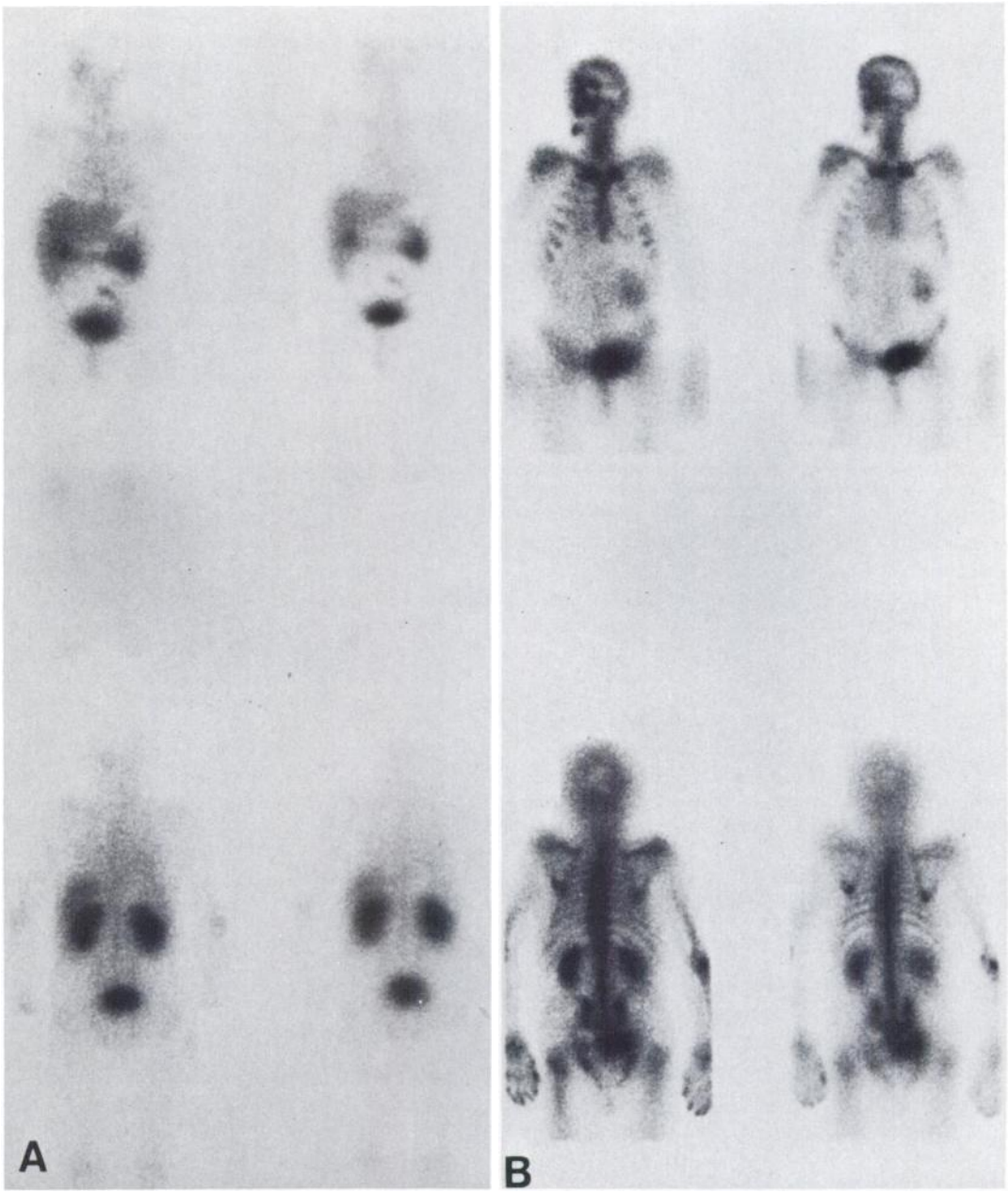

FIG. 3. Case 3 (A). Anterior and posterior skeletal PPi tomograms, obtained with Anger tomoscanner, show minimal bone uptake, with hepatic, renal, and soft-tissue activity. (B). MDP tomograms at same level show normal skeleton.

a severe inhibition of PPi uptake with little or no effect on the uptake of MDP.

Other possible causes of decreased bone uptake, including severe osteoporosis and thalassemia major (*18–19*), were not present in our patients, nor would they account for the normal visualization with MDP. A faulty tracer preparation is highly unlikely, since two of the three patients had more than one PPi scan on different occasions, always with nonvisualization, and several other patients injected from the same vial showed normal skeletal uptake.

At the time the bone scans were performed, no patient was receiving either chemotherapy or other chemicals known to alter the biodistribution of bone-scanning agents, such as urographic contrast medium (*20*), sodium gluconate, or calcium gluconate (*21*), so the possibility of a drug interaction with the tracer is unlikely. Serum protein electrophoresis in two of our patients gave no evidence of an abnormal protein that might bind the PPi.

Finally, partial extravasation at the injection site, as seen in cases 1 and 2, could contribute to decreased skeletal labeling, but, in our experience, would not cause such poor visualization. In addition, no extravasation was observed in the nonvisualizing previous scans of these patients, or in Case 3.

Regardless of the mechanism(s) involved, the practical implication of our cases is that in some patients, MDP may give results markedly superior to those of PPi. If a nondiagnostic scan is obtained with PPi, it should be repeated with MDP or possibly one of its analogs.

FOOTNOTES

* Technescan, Mallinckrodt.
† Tc-99m Medronate, Union Carbide.
‡ Tc-99m Medronate, Squibb.

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