CLINICAL EVALUATION OF ^{99m}Tc-LABELED MONOFLUOROPHOSPHATE: A COMPARISON WITH ETHANE-HYDROXY-DIPHOSPHONATE

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In preliminary clinical studies a new bone-scanning agent, ^{99m}Tc-labeled monofluorophosphate (MFP), provided satisfactory visualization of bone tumors. Comparison of MFP with EHDP shows, however, that because of higher tumor/bone ratios, lower blood activities, and more rapid whole-body excretion, EHDP remains the agent of choice at present.

Since the introduction of ^{99m}Tc-tripolyphosphate (*1*), many new phosphate bone-scanning agents have been described (*2–5*). We have compared ethane-hydroxy-diphosphonate (EHDP) [Diagnostic Isotopes (DII)], pyrophosphate (supplied by CIS), and two polyphosphates [New England Nuclear (NEN) and (DII)] in patients with malignant disease and normal controls. EHDP appears to be the most suitable of these four compounds (*6*). A ^{99m}Tc-labeled fluorine compound has shown promise in animal studies (*7*) and recently a new compound, ^{99m}Tc-labeled sodium monofluorophosphate (MFP), has become available for clinical evaluation. We have compared its performance with that of EHDP in patients and control subjects.

MATERIALS AND METHODS

A sodium monofluorophosphate/stannous fluoride preparation (MFP) is under development at the Radiochemical Centre (Amersham, Bucks., England) which kindly supplied experimental batches. MFP was supplied in bottles each containing a freeze-dried preparation of 100 mg MFP and 2 mg of stannous fluoride as reducing agent. For scanning studies 30 mCi of sodium pertechnetate ($^{99m}TcO_4^-$) in 7 ml was added to the bottle and 2 ml of the resulting solution injected intravenously after Millipore filtration (0.45-micron Millipore). Four hours after injection skeletal scintigrams were recorded on Polaroid film using a Nuclear Enterprises Scinticamera IV gamma camera. In this way 20 patients were studied. Visualization of the skeleton was satisfactory in all patients and there was no significant accumulation of isotope in any organ other than bone, kidney, and bladder. The scintigrams were sufficiently encouraging to stimulate us to compare quantitatively MFP and EHDP in 12 patients with known bony metastases and in 10 normal control subjects.

Twelve patients with x-ray-postive skeletal metastases were studied (nine breast, two lung, and one prostatic primary). Each patient was scanned on two separate occasions using an identical technique, 4 hr after the intravenous injection of 2 ml (8.58 mCi) of EHDP and MFP. In addition to Polaroid scans tumor/bone ratios were obtained using the multichannel analyzer. Tumor/bone ratios obtained with the two compounds from identical areas of the same patient were compared by paired Student's t-test, a method which we have previously used for intercomparison of ^{99m}Tc-phosphates (*6*).

To compare blood and whole-body levels of EHDP and MFP, ten healthy volunteers (male medical students) were studied. We have previously described a technique whereby hourly blood levels and hourly whole-body retention of injected 30 μCi ac-

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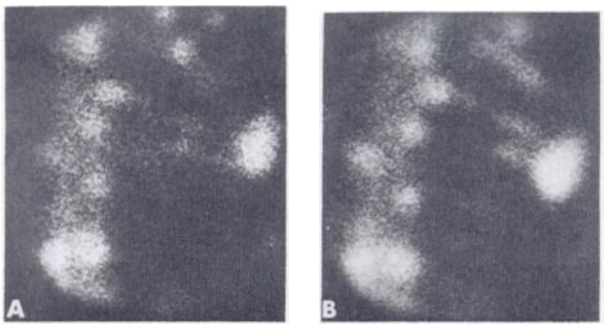

FIG. 1. Breast cancer: multiple metastases dorsal spine and ribs. (A) MFP; (B) EHDP.

TABLE 1. COMPARISON OF PROPERTIES OF EHDP AND MFP

	n	EHDP	MFP	P
Tumor/bone ratio	55*	1.82 ± 0.07	1.58 ± 0.06	<0.001
Blood level at 6 hr	10†	0.77 ± 0.06	1.21 ± 0.16	<0.02
Cumulative urine excretion at 6 hr	10†	79.88 ± 2.87	51.21 ± 2.21	<0.001
Whole-body level at 6 hr	10†	35.96 ± 1.47	56.48 ± 1.07	<0.001

All values = mean ± s.e.m., * n = number of tumors studied, † n = number of subjects studied, p = result of Student's t-test (paired with tumor/bone ratios, unpaired with other parameters), and $p < 0.05$ is considered significant.

tivities were compared in such subjects. The method gives accurate and reproducible results (*6*).

Each subject was given 30 μCi of MFP by intravenous injection. Whole-body activity was immediately measured using a shadow shield whole-body monitor (100% retention). Hourly thereafter both whole-body retention and blood activity (counted on a 5-ml venous blood sample and expressed as a percentage of injected activity per liter of blood) were measured. Whole-body and blood retention of MFP were compared with those of EHDP which had been measured previously in a similar control group (*6*). Results were compared by unpaired Student's t-test. Prior to the hourly whole-body count, the bladder was completely emptied and the voided urine was later counted using the lower detector of our whole-body monitor as a well scintillation counter. In this way cumulative hourly urine excretion of MFP was measured and compared with that of EHDP using an unpaired Student's t-test.

RESULTS

Visual comparison of the scans obtained with EHDP and MFP confirmed that metastases visualized with EHDP are also seen with MFP. EHDP scans were preferred, however, because the contrast between tumors and normal bone and between normal bone and background were better (Fig. 1). This subjective impression was confirmed by the paired Student's t-test, which showed that the tumor/bone ratios obtained with EHDP were significantly higher than those obtained with MFP (Table 1). When MFP is compared with the three other compounds which we have studied previously, it is clear that fluorophosphate offers no advantage with respect to higher tumor/bone ratios (mean ± s.e.m: MFP = 1.58 ± 0.06; pyrophosphate = 1.83 ± 0.08; NEN polyphosphate = 1.75 ± 0.09; DII polyphosphate = 1.68 ± 0.09).

Our previous work has shown that EHDP gives the lowest blood levels, highest urinary excretion, and lowest whole-body retention of all the ^{99m}Tc phosphates studied (*6*). For this reason we have compared in this paper the kinetics of MFP and EHDP only. To simplify the presentation further we have shown the results at 6 hr only although a similar pattern was noted throughout the study. Overall we have shown that urinary excretion of EHDP is significantly more rapid than that of MFP. Blood and whole-body levels are therefore significantly lower (Table1).

DISCUSSION

Fluoride ions have a strong affinity for the hydroxy apatite crystal of bone, and ^{18}F has been extensively used as a bone-scanning agent (*8*). The possibility of combining fluorine's high affinity for bone with the convenience of ^{99m}Tc is attractive. A ^{99m}Tc-Sn-F complex (Fluorotec) has been studied in rabbits and shows a similar concentration in bone to NEN polyphosphate (*7*). MFP contains both fluorine and phosphate and might therefore be expected to localize in high concentration in the skeleton. MFP is readily labeled with sodium pertechnetate in the presence of stannous fluoride and we have confirmed in 20 consecutive clinical studies that adequate visualization of the skeleton is possible. No toxic effects were noted.

A detailed comparison of the relevant characteristics show however that EHDP has definite advantages over MFP: tumor/bone ratios are significantly higher and blood (and therefore soft-tissue) levels are lower. These differences are clearly seen on the scintigram where better contrast is consistently obtained with EHDP. As differences in whole-body absorbed dose clearly depend on differences in biologic half-life, the more rapid excretion of EHDP is a further advantage. MFP is excreted from the body at a similar rate to NEN polyphosphate and gives blood levels similar to pyrophosphate but the tumor/bone ratios obtained with MFP are the lowest of the five compounds we have studied in detail.

Though it is conceptually attractive, we have concluded on the basis of the studies described here that MFP offers no advantage over EHDP, which remains our standard ^{99m}Tc-labeled bone-scanning agent.

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