A CONVENIENT, ECONOMICAL, AND HIGH-QUALITY SKELETAL-IMAGING AGENT

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An economical physiologic skeletal-imaging agent, \(^{99m}\text{Tc}-\text{Sn-pyrophosphate}\), preparable in convenient kit form is described. This radiopharmaceutical appears to manifest a distribution and target-to-background ratio comparable to other available \(^{99m}\text{Tc}\) bone imaging agents with the added benefits of using a physiologic molecule and being preparable in a stable and convenient lyophilized kit form.

The \(^{99m}\text{Tc}\) bone radiopharmaceuticals pioneered by Subramanian and others (1–6) have revolutionized skeletal imaging. Most of these compounds possess the drawbacks of being unphysiologic. Although linear polyphosphate polymers are susceptible to degradation by phosphoesterases such as alkaline phosphatases, these materials are not physiologic. Organic polyphosphate analogs, the diphosphonate group, are not enzymatically degraded in vivo and therefore have a long residence time in the body, primarily in the skeleton (7). The diphosphonates are known to be potent inhibitors of bone mineral crystallization and have been proposed for therapeutic use in metabolic bone disorders (8,9). Although diphosphonates are toxic, toxicity has only been observed at dose ranges considerably greater than those used for therapy and for skeletal imaging. Pyrophosphate, an anhydro-dimer of orthophosphate and the first member of the polyphosphate series, originally proposed for skeletal imaging by Perez, et al (6), has the advantage of being a physiologic molecule and susceptible to enzymatic degradation. Pyrophosphate is normally present in plasma in concentrations of 10 \(\mu\)moles/liter and is excreted in the urine in the range of 1–4 mg/day.

MATERIALS AND METHODS

Kit preparation. An 0.5-in. Teflon-coated bar magnet is placed in a sterile, pyrogen-free, 30-ml multi-dose vial along with 500 mg tetrasodium pyrophosphate decahydrate, AR-grade. Fifteen milliliters of water for injection are then added and the solution is stirred for 15 min under a sterile nitrogen purge or until the material is dissolved.

A stannous chloride solution containing 1.8 ml concentrated HCl and 126 mg anhydrous stannous...
One milliliter of stannous chloride solution is transferred into the pyrophosphate-containing vial using a 1-ml syringe and a needle with a plastic hub (not an aluminum-hubbed needle). This solution is well mixed, and the pH is assessed with a narrow range pH paper. If the pH is not between 3.0 and 3.5, it must be adjusted with N NaOH or HCl solution and the volume of concentrated HCl in the stannous chloride solution altered, making this step unnecessary in subsequent preparations. Hydronium ion concentrations greater than pH 3 can cause a rapid hydrolysis to orthophosphate depending on the temperature; pH values greater than 3.5 have led to visualization of gallbladder and colonic substance.

Next, 0.2 ml of 10% poloxymethylene (20) Sorbitan mono-oleate (polysorbate 80 USP) is added and mixed. This nonionic surfactant was found to be required to achieve complete solvation after lyophilization. This solution is dispensed in 0.5-ml aliquots through a 0.22-micron membrane filter into sterile 10-ml vacutainer tubes.

After prefreezing, the tubes are placed within 0.5 in. freeze-drier ports and lyophilized overnight. The tops are autoclaved for subsequent recapping. The freeze-drier vacuum is broken with a 0.22-micron filtered nitrogen flow through an unused port after which the tubes are aseptically recapped and refrigerated before use.

**Clinical studies.** The kits are reconstituted by addition of 30–45 mCi of 99mTc-pertechnetate, sufficient for three studies. Binding efficiency was determined by ascending paper chromatography using Whatman No. 1 paper and a solvent combination of acetone-30% acetic acid (7:3) giving Rf values of 0.9 (TeO2−), 0.05 (TSSP-Sn-Tc). The possibility of a technetium-bound colloidal component was evaluated by electrophoresis. Anodic migration rates of 14 cm/hr (TSSP-Sn-Tc), 10 cm/hr (TeO2−) at 300 volts d.c. resulted using cellulose polyacetate strips with a 0.06 M NaCl solution adjusted to pH 3.5 as the electrolyte. At no time from 1 to 4 hr after reconstituting the lyophilized kits had more than 1% ionic pertechnetate been found using the paper chromatography technique or more than 1% technetium-bound colloid been found at the origin of the electrophoretic strip. Two to 4 hr after intravenous injection of this 99mTc-pyrophosphate, patients are scanned with a whole-body scanner (Ohio-Nuclear Series-84) using two #17-L medium-energy, high-resolution Ohio-Nuclear collimators. Suspicious regions are further evaluated by scintiography (Nuclear-Chicago Pho/Gamma III HP) with the 250-keV fine-resolution, parallel-hole collimator. These kits have been used successfully as long as 4 hr after reconstituting with from 0.5 to

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*FIG. 2. Normal whole-body scan with 99mTc-pyrophosphate in 55-year-old woman.*

*FIG. 3. Whole-body scan with 99mTc-pyrophosphate in 72-year-old man with 10-year history of asymptomatic Paget's disease.*

chloride, AR-grade, is produced in a 10-ml volumetric flask with water for injection added to a total volume of 10 ml.
2 ml $^{99m}$Tc-pertechnetate solution without deterioration of the radiopharmaceutical.

RESULTS

The distribution of $^{99m}$Tc-pyrophosphate is similar to that of long-chain $^{99m}$Tc-polypophosphate and diposphonate as can be seen in two representative whole-body scans of normal subjects (Figs. 1 and 2). Similarly, the exquisite delineation of abnormal areas of $^{99m}$Tc-pyrophosphate uptake is readily apparent in two abnormal whole-body scans (Figs. 3 and 4). Suspicious regions in Fig. 4 were further evaluated by scintiphotography (Fig. 5). To date more than 100 such studies have been carried out in this laboratory. The lyophilized kits have demonstrated marked stability after periods of storage at 4°C up to 4 months. Capricious alterations in radiopharmaceutical distribution, such as colloid formation, have not been observed.

DISCUSSION

Bone-seeking $^{99m}$Tc-labeled radiopharmaceuticals are generally acknowledged to provide bone scans and scintiphotographs superior to those available with other agents, especially $^{18}$F. The physiologic $^{99m}$Tc-pyrophosphate prepared by this kit is an economical, stable, and convenient agent that provides uniformly excellent bone images.

FIG. 4. Posterior $^{99m}$Tc-pyrophosphate scan of 64-year-old man with metastatic lung carcinoma.

FIG. 5. Suspicious regions in Fig. 4 were further evaluated by scintiphotography denoting multiple areas of uptake consistent with metastatic disease.

REFERENCES