Letters to the Editor

RADIOCHEMICAL EVALUATION AND IMAGE CORRELATION OF STABILIZED AND NON-STABILIZED ^{99m}Tc-Sn-DIPHOSPHONATE KITS

In the December 1976 issue of the *Journal of Nuclear Medicine Technology*, McCormick, Sinclair, and Wahner have reported on the chromatographic quality and clinical correlation of three ^{99m}Tc bone-imaging agents *(1)*. We are in general agreement with the need and usefulness of performing radiochemical evaluations of commercial bone scanning kits, particularly with the increasing variety of available kits.

We have performed very similar radiochemical kit evaluations in the past *(2, 3)* and have achieved somewhat different results than McCormick et al. Our protocol was essentially similar and compared stabilized ^{99m}Tc-Sn-diphosphonate (^{99m}Tc-Sn-DIP) (Medi-Physics) and nonstablized ^{99m}Tc-Sn-diphosphonate (Diagnostic Isotopes) up to 4 h after preparation with 100-140 mCi of "instant" ^{99m}Tc-pertechnetate. We used a miniaturized double chromatography technique developed in our laboratory *(4)* which readily distinguishes between free ^{99m}Tc-pertechnetate, hydrolyzed reduced ^{99m}Tc, and ^{99m}Tc-DIP. Bone scans were performed 2.5–3.5 h after the administration of 20 mCi ^{99m}Tc-Sn-DIP and image quality was compared to the radiochemical purity determined at the time of injection.

The in-vitro instability of stabilized and nonstabilized ^{99m}Tc-Sn-DIP, as expressed by the formation of free ^{99m}Tc-pertechnetate, is shown in Fig. 1. Up to 6% and 9% of free ^{99m}Tc-pertechnetate were found in the non-stabilized preparation at 2 and 4 h, respectively, after radiopharmaceutical preparation. Less than 1% free ^{99m}Tc-pertechnetate was consistently found in stabilized kits up to 4 h after preparation. These data are in general agreement with the data of McCormick et al., who

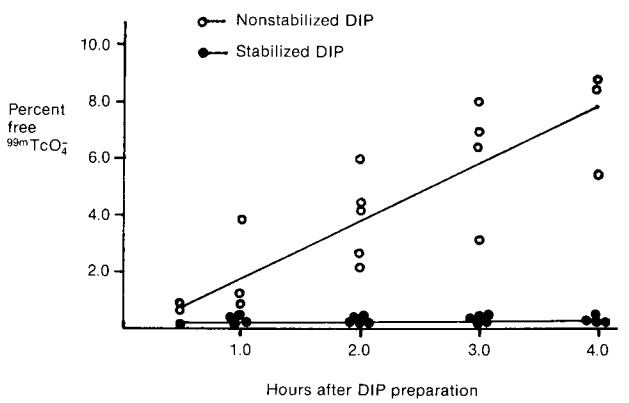

FIG. 1. In-vitro instability of stabilized and nonstabilized ^{99m}Tc-Sn-diphosphonate preparations as expressed by rate of formation of free ^{99m}Tc-pertechnetate.

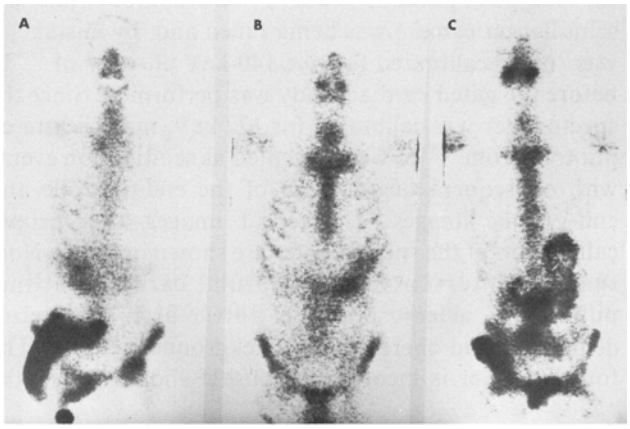

FIG. 2. Bone scans of selected patients using nonstabilized ^{99m}Tc-Sn-diphosphonate. (A) 0.5% (100 μCi) free ^{99m}Tc-pertechnetate level in radiopharmaceutical preparation at time of injection. (B) 3.3% (660) μCi) free ^{99m}Tc-pertechnetate in preparation at time of injection. (C) 7.5% (1.5 mCi) free ^{99m}Tc-pertechnetate in preparation at time of injection.

recommend not using the nonstabilized diphosphonate preparation after 2 h postformulation. Based on our data, we would restrict the use of nonstabilized diphosphonate kits even further, to 1 h.

Concerning the level of hydrolyzed reduced ^{99m}Tc, our study and the continual daily quality control of stabilized ^{99m}Tc-Sn-DIP in our laboratory have clearly shown that the hydrolyzed reduced ^{99m}Tc levels were consistently below 2%. The article by McCormick et al. shows much higher levels of hydrolyzed reduced ^{99m}Tc in bone scanning agents. The article does not clearly state whether paper chromatography (Whatman No. 1) or silica gel instant thin layer chromatography was used to determine hydrolyzed reduced ^{99m}Tc. In our experiences, we have found that a slight "hang-up" of activity can occur at the origin when using paper chromatography and normal saline, and this can result in a false high estimation of hydrolyzed reduced ^{99m}Tc. This type of an effect has also been mentioned by Colombetti et al. *(5)* when using heavier paper chromatography.

The bone scans obtained with nonstablilized ^{99m}Tc-Sn-DIP are presented in Fig. 2. The amount of free ^{99m}Tc-pertechnetate associated with Figs. 2(A), 2(B), and 2(C) was 0.5%, 3.3%, and 7.5%, respectively. Stomach uptake was observed on the bone scan having 3.3% free ^{99m}Tc-pertechnetate [Fig. 2(B)] at the time of injection. Very high stomach and intestinal activity was associated with the bone scan containing 7.5% free ^{99m}Tc-pertechnetate at the time of radiopharmaceutical injection [Fig. 2(C)]. We have observed stomach uptake at much lower concentrations (3.3% free ^{99m}Tc-pertechnetate) than those of McCormick et al. *(1)*, who have observed stomach uptake on bone scans with 15% free ^{99m}Tc-pertechnetate. Our clinical correlations demonstrate that for bone-

seeking radiopharmaceuticals stringent requirements should be considered concerning the labeling efficiency. Even a 95% labeling efficiency, which is equivalent to 1 mCi of free ^{99m}Tc-pertechnetate out of a 20-mCi ^{99m}Tc-Sn-DIP, can create unacceptable artifacts and, therefore, it seems advisable to consider higher labeling efficiencies for bone scanning radiopharmaceuticals.

References

1. McCormick MU, Sinclair MD, Wahner HW: Chromatographic quality of three ^{99m}Tc bone imaging agents. *J Nucl Med Technol* 4:189–192, 1976

2. Zimmer AM, Holmes RA: Radiochemical purity and stability of commercial Tc-99m-Sn-diphosphonate kits using a new chromatography technique. *J Nucl Med* 16: 584 (A), 1975

3. Zimmer AM, Pavel DG: Radiochemical evaluation of stabilized and non-stabilized Tc-99m-Sn-diphosphonate preparations and correlations to image quality. In *Abstracts of Annual Spring Meeting of Central Chapter*, Society of Nuclear Medicine, 1976

4. Zimmer AM, Pavel DG: Rapid miniaturized chromatographic quality control procedures for Tc-99m radiopharmaceuticals. In preparation

5. Colombetti LG, Moerlien S, Patel GC, et al: Rapid determination of oxidation state of unbound Tc-99m and labeling yield in Tc-99m labeled radiopharmaceuticals. *J Nucl Med* 17: 805–809, 1976

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REPLY TO "IMPURITIES IN A ^{99m}Tc-LUNG IMAGING KIT"

I would like to comment on the article "Impurities in a ^{99m}Tc Lung Imaging Kit," which appears on pp. 28-31 of this issue.

Organ distribution data in mice were presented in support of evidence obtained by thin layer chromatography that a substantial fraction of activity in the preparation was "dissociated from the macroparticles . . . The most significant radiochemical impurity present in the preparation was a ^{99m}Tc-protein which represented 12–14% of total radioactivity."

Results of organ distribution analysis as performed at New England Nuclear utilizing rats on NEN Pulmolite, Lot 7016, are presented in Table 1. In all cases the agent was prepared as described in the product labeling and the intact organs of interest assayed in a calibrated Capintec ion chamber.

TABLE 1. Organ Distribution Analysis in Rats

Organ	Distribution (percent injected dose, decay corrected) 15 min (n = 4)	24 h (n = 6)
Lung	91.6% Range: 90.5–93.3	3.1% Range: 2.2–4.2
Liver	1.1% Range: 1.0–1.3	13.1% Range: 11.1–14.4
Carcass	4.1% Range: 3.8–4.8	5.8% Range: 5.2–7.1
Spleen	0.1% Range: 0.0–0.1	1.7% Range: 1.3–2.5
Blood	1.1% Range: 0.9–1.1	0.9% Range: 0.8–1.1

All lots of Pulmolite manufactured to date have shown a *distribution of 85–95% of the injected dose to the lung at 15 min postinjection,* decay corrected. These results are, in my opinion, entirely consistent with an efficacious agent and are, of course, consistent with the requirements of the XIX edition of the *United States Pharmacopoeia.*

The organ distribution data presented by the authors in their Table 3 in support of the proposition that a soluble protein fraction is radiolabeled to an appreciable extent are, in my opinion, inadequate to justify the latter conclusion.

A radiolabeled soluble protein would distribute principally to blood, kidney, and bladder, *and the distribution of activity to these organs, as observed by the authors, clearly does not parallel the decline in observed distribution to lung over 1 h.*

The authors further report the relative distribution of activity to the kidney and lungs in human patients injected with NEN's ^{99m}Tc-stannous macroaggregated albumin. Region-of-interest studies in four patients reported to us from the Boston Children's Hospital describe a kidney distribution of activity of 2.5–7.5% of the injected dose (personal communication from Michael Davis).

In summary, we believe that further work should be done to correlate the in-vitro results reported by the authors with clinical observations and with animal distribution studies. The experimental distribution of activity described by the authors for the mouse may suffer from technique-related issues including questions of counting geometry and/or large dilutions of the labeled kit, beyond those demonstrated to be consistent with kit efficacy.

It is our belief that the agent should be prepared according to the manufacturer's instructions when such an investigation is conducted. It is my understanding on