Radiopharmacy

Unit Dose Radiochemical Stability of Commonly Used Technetium-99m Radiopharmaceuticals

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The use of radiopharmaceuticals as unit doses that may be prepared several hours before injection prompted this analysis of the radiochemical purity of radiopharmaceuticals held in plastic syringes versus glass vials. Four of the five radiopharmaceuticals studied maintained > 90% binding up to and in some cases exceeded the manufacturer's stated expiration time in both plastic and glass containers. In all cases the radiochemical purity was higher in the glass vial than the plastic syringe for up to 24 hr after preparation.

Many nuclear pharmacies dispense radiopharmaceuticals in plastic syringes as unit doses. Unit dose radiopharmaceuticals often remain in syringes for hours before arrival and administration at their destinations, and no radiochromatography is performed just before injection into the patient. When stored in syringes, not only has the storage material been changed from the glass of the preparation vial, but the dose concentration may be altered compared to the solution in the preparation vial. It is the responsibility of a nuclear pharmacy to assure its customers that these preparations still meet the United States Pharmacopeia and National Formulary (USP-NF) standards at their calibration time.

To ascertain this standard, quality control procedures are performed routinely in our nuclear pharmacy before radiopharmaceuticals are dispensed. One procedure measures radiochemical purity, which is defined as "the fraction of a specific radioisotope that is present in the desired form" (*1*). Radiochemical impurities can produce imaging artifacts, creating false positive or false negative images. Probably, the most common radiochemical impurity encountered is that of free pertechnetate in ^{99m}Tc-labeled compounds. Injection of a ^{99m}Tc-labeled radiopharmaceutical containing large amounts of free pertechnetate produces image artifacts in the form of stomach, thyroid, and salivary gland uptake. Unwanted localization of free pertechnetate can mask areas of interest in other diagnostic procedures. For example, during bone imaging, uptake of free pertechnetate in the stomach may hide rib and spinal lesions, and salivary gland uptake could be mistaken for mandibular lesions. Furthermore, radiochemical impurities may alter the critical organ dose and change the biodistribution and lead to image quality degradation (*1*). In essence, the benefit versus risk ratio is lowered (*2*). Results of this testing must meet the standards established by the USP-NF which currently has set the requirement for most ^{99m}Tc products at 90% radiochemical purity (*2*). These standards are based upon blood clearance rates, excretion rates, the physical half-life of the radionuclide used, the biological half-life of the radiopharmaceutical, and the extent of the impurities (*1*).

Radiochromatography is the most commonly accepted method for determining radiochemical purity in the nuclear pharmacy. Various chromatographic techniques have been evaluated for radiochemical purity testing ranging from sophisticated column chromatography to simple paper chromatography (*1-6*). Instant thin layer chromatography (ITLC) is currently the method of choice for purity testing of radiopharmaceuticals.

Several studies in the past have been done with primary emphasis on radiochemical purity of certain radiopharmaceuticals. Krogsgaard (*7,8*) had two such studies published in 1976 using ^{99m}Tc sulfur colloid as the subject of one study and ^{99m}Tc bone agents for the second. In 1981, Zbrzeznj and Khan (*9*) published a similar stability study of ^{99m}Tc glucoheptonate. These investigators conclude that time is an important factor in radiopharmaceutical breakdown but mention very little about storage systems.

Radiochromatography for free pertechnetate content was carried out on five of the ^{99m}Tc radiopharmaceuticals routinely used by our regional nuclear pharmacy.

MATERIALS AND METHODS

Radiochromatography was performed on control prepara-

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tions in the glass vial as well as doses stored in a plastic unit dose syringe. The following radiopharmacuetical kits were evaluated:

1. HDP oxidronate,*
2. pyrophosphate,†
3. macroaggregated albumin (MAA),‡
4. disofenin,§
5. DTPA (Sn) chelate.¶

Pertechnetate was freshly eluted from a ^{99m}Tc generator and kits were prepared according to manufacturers' package inserts (*10–14*) and standard nuclear pharmacy protocol. No total kit activity exceeded the manufacturer's recommended limits. All unit doses were prepared in volumes and activities suitable for patient dose administration.

Two separate runs on each radiopharmaceutical used four kits of the same radiopharmaceutical prepared in the same manner at the same time. Pertechnetate used for the four kits was all from the same elution. One vial was set aside as a control vial, the remaining three vials were considered the experimental solutions. Eleven unit doses in volumes and activities suited for patient administration were drawn from each of the three experimental vials into 3-ml sterile plastic disposable syringes. The syringes were stored with their original 22-gauge needle and cap in place after loading the radiopharmaceutical.

Radiochromatography using ITLC techniques was performed on a syringe from each vial and a sample from the control vial immediately after preparation and every hour for 8 hr. Subsequent chromatography was also performed at 12 and 24 hr. Radiochromatography strips were spotted in duplicate.

The chromatographic technique consisted of spotting the radiopharmaceutical on 1 cm × 9 cm ITLC-Silica gel strips at the origin, 1 cm from the end. ITLC-Silicic acid strips of the same size were used for disofenin. After spotting, the strips were placed in 0.5 cm of developing solution in a 1.5 cm × 11 cm test tube, and a stopper was placed in the test tube. The solvent front was allowed to reach 0.5 cm from the top of the strip. Methyl ethyl ketone was the developing solvent for all radiopharmaceuticals except disofenin where 20% saline was used.

The strips were removed from the developing solvent, allowed to dry, and placed in a dose calibrator where the total activity of the strip was measured in microcuries. Then the strip was cut in half and the activity of the lower half containing the bound fraction was measured in the dose calibrator. Because free pertechnetate should move along the solvent front and the bound ^{99m}Tc complex should remain at the origin, the following formulas were used to find percentage bound and free (*2*).

$$\% \text{ Bound} = \frac{(\text{Activity bound} - \text{Bkg}) \times 100}{(\text{Total activity} - \text{Bkg})}$$

$$\% \text{ Free} = 100 - \% \text{ Bound}$$

RESULTS

The average chromatography results in percentage bound of the five radiopharmaceuticals investigated are summarized in Table 1. Each manufacturer's suggested use of the radiopharmaceutical after preparation is 6 hr, except oxidronate which is 8 hr, and DTPA (Sn) chelate which is < 1 hr for glomerular filtration rate determinations (*10–14*). All of the tested radiopharmaceuticals except one remained stable (i.e., 90% radiochemically pure) in both forms throughout the manufacturer's recommended expiration time, and many remained stable much longer. Pyrophosphate was stable for 8 hr in the vial, but only lasted 4 hr in a unit dose situation, therefore falling short of the manufacturer's stated shelf life of 6 hr. Oxidronate

TABLE 1. Evaluation of Unit Dose Versus Vial Storage of Radiopharmaceutical Breakdown (percent bound)

	Radiopharmaceutical									
	HDP Oxidronate		Pyrophosphate		MAA		Disofenin		DTPA (Sn) Chelate	
Time (hr)	Vial	Unit Dose	Vial	Unit Dose	Vial	Unit Dose	Vial	Unit Dose	Vial	Unit Dose
0	99.9 ± 0.2	99.5 ± 0.7	97.9 ± 3.0	98.5 ± 1.3	99.8 ± 0.3	99.3 ± 0.8	99.7*	99.4 ± 0.8	99.4 ± 0.9	99.5 ± 0.6
1	99.2 ± 0.8	99.2 ± 0.7	98.4 ± 0.4	98.8 ± 0.9	98.9 ± 1.6	98.9 ± 0.8	100.0	99.2 ± 0.7	99.5 ± 0.1	98.5 ± 1.2
2	99.8 ± 0.4	99.6 ± 0.5	99.1 ± 0.1	99.0 ± 0.7	99.6 ± 0.1	99.1 ± 0.6	99.6	99.1 ± 0.5	99.4 ± 0.8	97.3 ± 2.4
3	99.4 ± 0.1	98.9 ± 1.1	99.3 ± 0.6	95.6 ± 4.0	99.5 ± 0.4	99.1 ± 1.2	99.5	97.2 ± 1.2	99.7 ± 0.4	95.6 ± 2.4
4	98.6 ± 0.6	99.2 ± 0.5	97.0 ± 1.8	90.9 ± 5.2	99.0 ± 1.5	98.4 ± 1.0	98.9	96.2 ± 0.9	99.3 ± 0.4	95.8 ± 2.2
5	99.4 ± 0.3	97.8 ± 1.3	98.9 ± 0.9	84.3 ± 14.4	99.3 ± 1.1	98.9 ± 0.6	98.9	94.9 ± 1.9	97.5 ± 3.0	95.2 ± 1.6
6	99.5 ± 0.1	97.9 ± 1.1	99.0 ± 0.7	71.2 ± 19.4	98.8 ± 0.4	98.6 ± 0.7	98.5	93.7 ± 2.4	96.9 ± 2.1	93.3 ± 4.6
7	99.0 ± 0.4	96.5 ± 1.2	98.4 ± 1.4	68.5 ± 24.6	99.3 ± 0.6	98.2 ± 1.4	98.5	91.4 ± 2.5	96.0 ± 0.8	89.9 ± 5.7
8	98.1 ± 1.4	94.9 ± 2.1	97.4 ± 1.6	46.5 ± 14.8	98.4 ± 1.6	98.0 ± 1.6	97.8	88.6 ± 2.9	96.0 ± 2.3	92.9 ± 2.7
12	94.8 ± 1.2	92.4 ± 0.8	79.6 ± 25.7	27.9 ± 5.6	98.7 ± 0.9	97.7 ± 1.7	97.3	75.3 ± 6.2	93.5 ± 2.2	87.9 ± 2.4
24	89.7 ± 1.2	87.5 ± 2.4	37.0 ± 19.6	19.4 ± 5.3	96.4 ± 1.5	97.6 ± 1.4	85.7	57.9 ± 7.0	88.3 ± 6.1	82.6 ± 2.2

*Because of expired reagents, the results of the first run of disofenin were considered invalid and all results are based on the second run only.

was found to be radiochemically useable up to 12 hr after preparation in both the vial and unit dose. MAA remained stable up to 24 hr in both vial and unit dose forms. The DTPA (Sn) chelate was stable in the vial up to 12 hr and began to break down in the unit dose form at about 6 hr. Disofenin showed vial stability lasting 12 hr and unit dose stability ending at $\sim$ 8 hr.

Paired *t*-tests on each radiopharmaceutical indicated that only MAA was stable from the time of preparation up to 24 hr. Student's *t*-test was performed to find the time when vial or unit doses began to break down. Oxidronate radiochemically began disintegrating between 4 and 5 hr ($p < 0.001$) in the unit dose, and there was a significant difference ($p < 0.001$) between the radiochemical purity of the unit dose at preparation and 8 hr, whereas no difference was seen in the vial purity. Between 2 and 3 hr ($p < 0.01$) pyrophosphate and disofenin unit doses started deteriorating. No difference was shown in vial purity between 0 and 6 hr but there was a difference in unit dose ($p < 0.001$). Although DTPA (Sn) chelate unit doses did not begin to break down until between 8 and 12 hr ($p < 0.001$), there was a significant difference between unit doses at 0 and 1 hr ($p < 0.05$) and 0 and 6 hr ($p < 0.001$).

DISCUSSION

Sources of radiochemical impurities can be grouped into two classes: 1) radiochemical impurities resulting from synthesis and production of the radiopharmaceutical; and 2) breakdown during storage. For the commercial nuclear pharmacy and nuclear medicine department hot lab, production and synthesis impurities should be of no consequence if manufacturers' kits are prepared as directed and routine quality control procedures are maintained. However, radiochemical breakdown during storage may pose a threat to the nuclear pharmacy and hospital nuclear medicine department.

The major cause of breakdown during storage is radiation-induced decomposition that occurs as the result of the deposition of many thousands of keV of energy in the radiopharmaceutical (*1*). This energy can cause the lysis of chemical bonds, and as the radiopharmaceutical volume is usually small, this effect can be significant. Primary radiolysis occurs within the molecule where the disintegration occurred, whereas secondary radiolysis occurs in other nearby molecules. The specific activity of the radiopharmaceutical and the amount of energy absorbed by the solution directly control the extent of radiolysis. Chemists have discovered some additives to control radiolysis, such as electron scavengers, but these only control secondary radiolysis (*1*). It has also been found that decreasing oxygen content has improved the stability of some radiopharmaceuticals, leading experts to believe that this reduces radiolysis.

Chemical decomposition is also responsible for breakdown during storage. Chemical decomposition occurs independently of radioactive decay and unlike radiolysis, usually only results in the separation of the radioactive label from the tagged compound. Many different chemical reactions are responsible for this phenomena—hydrolysis, chemical reaction, reaction with the carrier, competitive chelation, and equilibration with the carrier (*1*). Hydrolysis reactions are usually pH dependent and also depend upon the medium in which the radiopharmaceutical is prepared. Other chemical substitutions can be brought about by catalysts such as hydroxyl and siloxyl groups, which are found on the surfaces of glass containers. Therefore, chemical decomposition can be kept to a minimum by preparing and storing radiopharmaceuticals in the proper buffers and vials (*1*).

Many factors influence the other forms of chemical decomposition. Temperature influences endothermic chemical reactions; therefore, increased storage temperatures may enhance this form of breakdown. However, temperatures that are too low may destroy some large biologic molecules or cause insolubility. Additives such as bacteriostatic agents and radiolysis scavengers may also react with the radiopharmaceutical preparation. Because of the low concentration of tracer in most radiopharmaceuticals, other chemicals may readily combine with molecules in the radiopharmaceutical. reactions of this type are unpredictable and are particularly troublesome (*1*).

The transtition metal chelates are subject to a special type of chemical decomposition. Free ligands and metal are in equilibrium with the chelation compound; therefore, other metals with the same charge and other similar ligands will be in competition for binding sites. Chemical composition of the solution needs to be carefully monitored to detect these reactions (*1*).

After investigating the actual mechanisms of chemical breakdown during storage, it is easy to see that the longer the radiopharmaceutical is stored, the greater the radiochemical breakdown.

CONCLUSION

Some recommendations for storage and use of radiopharmaceuticals can be based on the results of this study. As most unit doses are stable for the current recommended useable time, unit dose dispensing is safe and practical. However, because there is a slight tendency for unit preparations to break down faster, it would be wise to store unit doses no longer than necessary. It would also be helpful for a nuclear pharmacy to routinely perform a testing procedure such as this one on all radiopharmaceuticals prepared in the pharmacy. Such a screening procedure would ensure that no changes have occurred in the kits supplied by commercial suppliers. If discrepancies are found, as in the case of pyrophosphate, it would be beneficial to keep storage times minimal for both unit dose and vial preparations. Routine monitoring of these radiopharmaceuticals is vital. It should be noted that this study was carried out under ideal conditions, with no unusual changes in the physical environment.

Studies such as this could be the ground work that will influence other areas of nuclear pharmacy. Although this study provides no conclusive evidence of any specific differences in breakdown in the unit dose and vial systems, it does indicate a need for further analysis of different radiopharmaceutical storage materials. It also stands to reason that more

sophisticated analysis of breakdown mechanisms is easier to achieve if we know when the breakdown occurs. If radiopharmaceuticals are consistently found to be stable for longer periods of time, the issue of maintaining sterility can be addressed. If methods of maintaining sterility are proven and the compounds are stable, the nuclear pharmacy can reduce costs and extend these cost reductions to its clients. In this era of cost conscious medicine, all of these improvements can lead to an overall savings.

FOOTNOTES

*Osteoscan-HDP oxidronate, Mallinckrodt Inc., St. Louis, MO.
†Pyrolite pyrophosphate, Du Pont Co., N. Billerica, MA.
‡Pulmolite, Du Pont Co., N. Billerica, MA.
§Hepatolite disofenin, Du Pont Co., N. Billerica, MA.
¶DTPA (Sn) chelate, Medi-Physics, Inc., Richmond, CA.

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