Radiation Decomposition of Technetium-99m Radiopharmaceuticals

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Technetium-99m radiopharmaceuticals are shown to be subject to autoradiation-induced decomposition, which results in increasing abundance of pertechnetate in the preparation. This autodecomposition is catalyzed by the presence of oxygen, although the removal of oxygen does not prevent its occurrence. The initial appearance of pertechnetate in the radiopharmaceutical is shown to be a function of the amount of radioactivity, the quantity of stannous ion used, and the ratio of Tc-99m to total technetium in the preparation.

J Nucl Med 20: 138–143, 1979

There have been several references in the literature (*1,2*) indicating that once technetium-99m radiopharmaceuticals are labeled they are not subject to atmospheric oxidation. This is contrary to our own observation, which is basically similar to that reported by Tofe and Frances (*3*), in that whereas the initial quality control may indicate excellent labeling, repeat testing done several hours after preparation occasionally shows much lower labeling efficiencies. Lyster (Lyster D., personal communication) indicated that the stability of the technetium label appeared to be dependent on radioactivity. Vesely and Cifka (*4*) showed that under the appropriate conditions pertechnetate can be reduced by gamma radiation, resulting in failure of elution from alumina columns. Lefort (*5*) has reported that pertechnetate is not reduced by gamma radiation but rather that Tc(IV) is oxidized.

This paper is an attempt to investigate the influence of the radioactivity on the stability of Tc-99m radiopharmaceuticals.

Received Dec. 29, 1977; revision accepted Oct. 9, 1978.

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MATERIALS AND METHODS

The [^{99m}Tc] pertechnetate used throughout this work was obtained from our liquid-liquid extraction system and subjected to our test for the presence of oxidants (*6*). Only when this test was absolutely negative, corresponding to less than 10^{-6} *M* solutions of hypochlorite or peroxide, was the pertechnetate used in these experiments.

Series A. The chemical technetium content was kept constant at 5×10^{16} atoms by using 15 ml of the initial elution after reloading the liquid-liquid extraction system. This is calculated as follows:

1. The buildup of Tc-99 during the 4-day irradiation of molybdenum-98 to form the parent molybdenum-99 is calculated from the equations:

$$\frac{dN_1}{dt} = Q - \lambda_1 N_1$$

$$\frac{dN_2}{dt} = \alpha\lambda_1 N_1 - \lambda_2 N_2$$

$$\frac{dN_3}{dt} = (1 - \alpha)\lambda_1 N_1 + \lambda_2 N_2,$$

where $N_1N_2N_3$ are the numbers of atoms of Mo-99, Tc-99m, and Tc-99, respectively, and λ_1 and λ_2 are the decay constants of Mo-99 and Tc-99m. For the purpose of this calculation, Tc-99 was considered stable, α is the fraction of disintegrations of Mo-99 resulting in Tc-99m, and Q is the rate at which Mo-99 is formed. The solution of these equations for a 4-day irradiation gives 0.153 as the mole fraction of Tc-99m—that is, the fraction of technetium in the metastable form.

2. There is a further buildup of Tc-99 between the end of bombardment and the first elution, a period of 3.5 days. If this is calculated as done by Lawson et al. (7), the resultant fraction in the metastable form is 0.0314.

Since the 15-ml of elutant from the initial milking contained about 1.37 curies of Tc-99m, and since one curie of "carrier-free" Tc-99m contains 1.15×10^{15} atoms of Tc-99, there will be about 5×10^{16} atoms of technetium in 15 ml.

In each preparation, 15 ml of such an elution was used in a total volume of 20 ml. The actual radioactivity was varied by mixing an extraction obtained that day with decayed material from the week before.

Series B. The ratio of Tc-99m to total Tc was maintained at 0.25 (7) by using an extraction obtained from a unit in which the previous extraction cycle had been done 21 hr earlier, then allowing the product to decay for 1 hr following separation from the parent Mo-99. Since extraction efficiencies are over 95% of theoretical yield, any carryover of technetium from previous extractions is ignored. (The extraction immediately following the initial extraction, Series A, was not used.) In this series one curie would contain 4.6×10^{15} atoms of technetium.

Series C. The ratio of Tc-99m to total technetium was maintained at 0.60 (7) by using an extraction obtained from a unit in which the previous extraction cycle had been performed 3 hr earlier, then allowing the product to decay for 1½ hr following separation from the parent molybdenum. In this series one curie would contain 1.92×10^{15} atoms of technetium.

The study was carried out on three different technetium radiopharmaceuticals prepared according to our standard protocols as follows.

1. *Technetium-99m pyrophosphate.* Two milliliters of 2.5% w/v sodium pyrophosphate decahydrate are combined with 15 ml of pertechnetate solution and 3 ml of 0.25 *N* acetic acid. This solution is then electrolyzed between tin electrodes for 10 min with a 4-mA current, which produces 1.5 mg of stannous ion. The electrodes were removed immediately and the product allowed to stand for 15 min, then filtered through a 0.22-micron filter into a multidose vial. This final filtration was included to simulate normal radiopharmaceutical production, although checks of the filter showed no significant retention of technetium, and preparations in which filtration was omitted behaved in an identical manner.

2. *Technetium-99m gluconate.* Five hundred milligrams of calcium gluconate in 5 ml of solution are added to 15 ml of pertechnetate solution and electrolyzed between tin electrodes for 10 min with a 4-mA current, producing 1.5 mg of stannous ion. The electrodes were immediately removed and the product allowed to stand for 15 minutes before being filtered through a 0.22-micron filter into a multidose vial.

3. *Technetium-99m human serum albumin.* One hundred and ten μl of 25% salt-poor human serum albumin were mixed with 15 ml of pertechnetate and 0.44 ml of *N* hydrochloric acid, then electrolyzed between tin electrodes for 10 min with a 2-mA current, producing 0.75 mg of stannous ion. The electrodes were immediately removed, 2.2 ml of 10% dextrose and 2.2 ml of a sodium acetate buffer (pH 5.6) were added, and the product was allowed to stand for 15 min before filtration through a 0.22-micron filter into a multidose vial.

Immediately after the final filtration, and again 4 hr later, chromatographic analysis was performed on each preparation to evaluate the level of pertechnetate, using thin-layer chromatography on silica gel with methyl ethyl ketone as solvent.

Time dependence of the radiolytic decomposition. To investigate the time dependence of the radiolytic decomposition of Tc-99m pyrophosphate, a preparation containing 570 mCi of pertechnetate with a

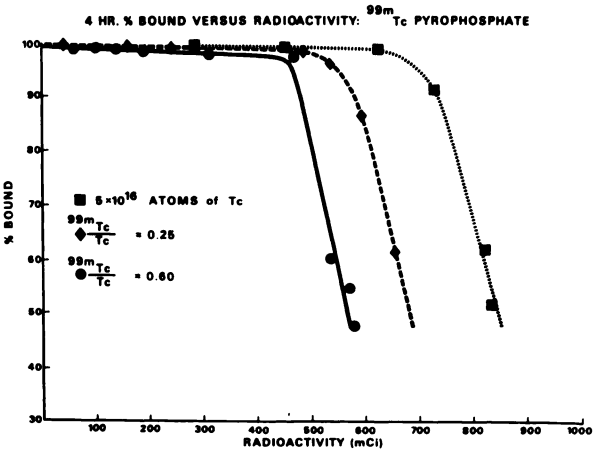

FIG. 1. Percentage of Tc-99m bound to pyrophosphate at 4 hr against initial level of radioactivity. All preparations had better than 98% bound immediately after preparation.

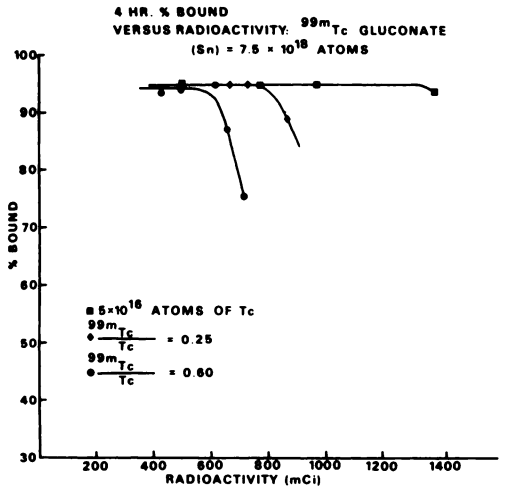

FIG. 2. Percentage of Tc-99m bound to gluconate at 4 hr against initial level of radioactivity. All preparations had better than 98% bound immediately after preparation.

Tc-99m/Tc ratio (Tc-99m to total Tc) of 0.6 (i.e., series C) was analyzed for pertechnetate on an hourly basis for 5 hr after preparation.

Effect of oxygen on the radiolytic decomposition. The effect of oxygen on the radiolytic decomposition of Tc-99m pyrophosphate was studied by each of the following.

1. An 850-mCi preparation containing 5×10^{16} atoms of technetium (i.e., series A) was flushed with nitrogen gas for 10 min following filtration.

2. Oxygen was continuously bubbled through 200-mCi, 400-mCi, and 480-mCi preparations made with pertechnetate having a Tc-99m/Tc ratio of 0.60 (i.e., series C).

3. Several Series B pyrophosphate preparations (Tc-99m/Tc = 0.25) were prepared with half the quantity of stannous ion (2-mA for 10 min), with nitrogen flushing of all reagents before use and of the final preparation for 10 min.

Effect of stannous ion content on radiolytic decomposition. The dependence of the stability on the quantity of stannous ion was investigated by preparing a number of Series B pyrophosphate preparations (Tc-99m/Tc = 0.25) but electrolyzing them for 10 min at 1 mA, 2 mA, or 3 mA—i.e., with only ¼, ½, or ¾ of the amount of stannous ion in the standard preparation.

Effect of external irradiation by 140-keV photons. To investigate the effect of 140-keV radiation on radiopharmaceutical preparations, one-ml samples of Tc-99m pyrophosphate with low radioactive concentration were placed in a thin-walled glass tube and immersed in 20 ml of pertechnetate solution with a radioactivity of up to 2.5 curies.

Evaluation of electrolytically-generated stannous ion. To ensure that the differing reaction conditions were not affecting the quantity of stannous ion generated per unit electrical charge, each radiopharmaceutical reaction mixture was electrolyzed between a pair of weighed tin electrodes for a period of 1 hr at the appropriate current. The electrodes were then reweighed and the weight loss compared with the theoretical weight of stannous ion generated. In all cases agreement was within 5%.

RESULTS AND DISCUSSION

In all cases, the initial labeling was better than 98%, i.e., there was less than 2% pertechnetate.

Technetium-99m pyrophosphate. The results of the 4-hr pertechnetate determinations for all three Tc concentrations in the pyrophosphate are shown in Fig. 1. Note that no precautions were taken to remove oxygen from the multidose vials or the solutions used. The graph shows that good 4-hr stability of the pyrophosphate is obtained up to a certain critical radioactivity, but that once this level is exceeded the amount of pertechnetate present 4 hr after preparation increases rapidly with small increases in the radioactivity.

Technetium-99m gluconate. The results for the Tc-99m gluconate are shown in Fig. 2. There is an obvious similarity between these results and those for Tc-99m pyrophosphate, the major difference being that all the "critical radioactivities" are somewhat higher, indicating a greater resistance of this product to radiation-induced oxidative decomposition.

Technetium-99m human serum albumin. The results for the Tc-99m HSA are shown in Fig. 3. Again the pattern of the previous two radiopharmaceuticals is repeated, although the critical values

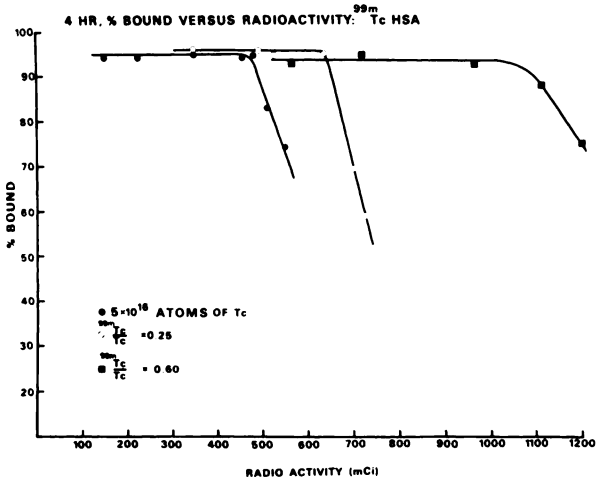

FIG. 3. Percentage of Tc-99m bound to human serum albumin at 4 hr against initial level of radioactivity. All preparations had better than 98% bound immediately after preparation.

are different. It should be mentioned, however, that the level of stannous ion used was only half that used in the pyrophosphate and gluconate studies. This was done because the 1.5 mg of stannous ion used in the pyrophosphate and gluconate studies was above the amount we would normally use in a technetium albumin preparation, and initial studies indicated that at these higher levels of tin no radioation decomposition would be observed within the 4 hr at radioactivity levels that we could reach.

Note that for the three radiopharmaceutical studies the "critical radioactivity" is dependent on the total technetium content, the preparations containing more technetium being more resistant to Tc-99m radiation effects. This effect would appear not to be one of total reductant present, since in all preparations the total reducing capacity is supplied by the initial stannous ion. This was the same for all and had a molar concentration over 100 times that of the highest technetium concentration. Table 1 shows the total technetium content at the critical radioactivities for each of the three radiopharmaceuticals. An examination of these figures shows that the "critical radioactivity" is a logarithmic function of the quantity of technetium in the preparation.

Time dependence of the radiolytic decomposition. Figure 4 shows the results of the radiolytic time-course study on a 570-mCi preparation of Tc-99m pyrophosphate in series C. The pertechnetate starts to appear early: after only 2 hr there is a significant amount of pertechnetate, despite the indication in Fig. 1 that a 465-mCi preparation shows no radiolytic breakdown after 4 hr. Thus it is obvious that the radiolytic breakdown is dose-rate dependent rather than total-dose dependent.

The effect of oxygen on the radiolytic decomposition. In the study of the effect of oxygen, the 850-mCi technetium pyrophosphate preparation (series A), which was flushed with nitrogen for 10 min, showed no radiolytic decomposition after 24 hr compared with a value of 50% pertechnetate in 4 hr for a similar preparation that was not flushed with nitrogen (Fig. 1). This clearly indicates that oxygen has a critical role in the radiolytic decomposition process. On the other hand, a 200-mCi technetium pyrophosphate preparation (Series C), through which oxygen was continuously bubbled, showed no radiolytic decomposition in 4 hr. A 400-mCi preparation showed 4% free pertechnetate after 5 hr. A 480-mCi preparation from this oxygen series showed 11% free pertechnetate after 4 hr. This value lies on the Series C curve in Fig. 1, suggesting that the bubbling of oxygen through the solution does not enhance the radiolytic decomposition rate over that which occurs in a normal solution under atmospheric oxygen. A similar effect is well established in radiation therapy, where it is referred to as the oxygen enhancement ratio and has been found to saturate at an oxygen partial pressure of 30–40 mm of Hg (*8*).

Figure 5 shows the results obtained from the 4-hr stability studies on the preparations containing only half of the quantity of stannous ion and flushed with nitrogen gas. This curve is of the same shape as the curves in which no nitrogen flushing was

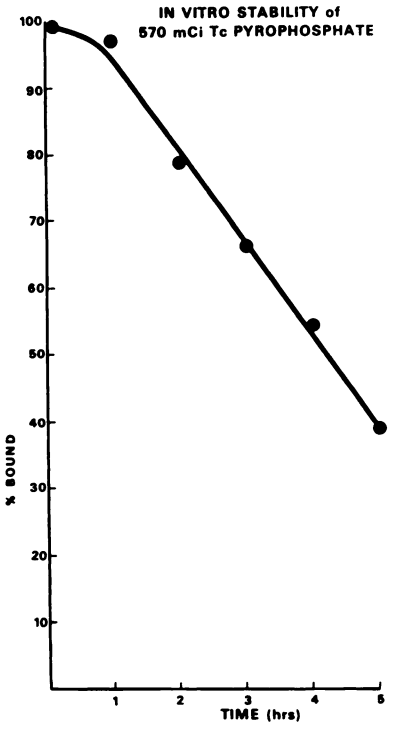

FIG. 4. Percentage of Tc-99m remaining bound to pyrophosphate as a function of time after preparation.

TABLE 1. CHEMICAL TECHNETIUM CONTENT AT THE CRITICAL RADIOACTIVITIES

Critical radioactivity	Technetium content (atoms)	Log (Tc)
Pyrophosphate		
700	50×10^{15}	16.699
550	2.53×10^{15}	15.403
450	0.86×10^{15}	14.937
Gluconate		
1350	50×10^{15}	16.699
800	3.68×10^{15}	15.566
600	1.15×10^{15}	15.061
Human serum albumin		
1050	50×10^{15}	16.699
650	2.99×10^{15}	15.476
450	0.86×10^{15}	14.937

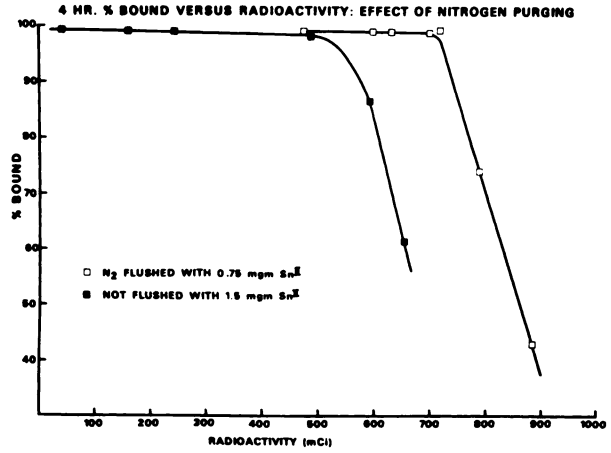

FIG. 5. Effect of nitrogen flushing on 4-hr stability of Tc-99m pyrophosphate preparation. Although the nitrogen-flushed preparations contain only half as much stannous ion, they have greater % bound after 4 hr. All preparations had greater than 98% bound immediately after preparation.

used, but the "critical radioactivity" is approximately 700 mCi as compared with only about 550 mCi for the preparation that was not nitrogen-flushed, despite the fact that only half the Sn was employed in the nitrogen-flushed preparation. Clearly, therefore, the removal of oxygen from the system helps to reduce, but does not prevent, the radiation decomposition of the radiopharmaceutical.

Effect of stannous ion content on the radiolytic decomposition. The dependence of the stability of the radiopharmaceutical on the quantity of tin used is clearly observed in Fig. 6, which shows the 4-hr stability as a function of radioactivity for stannous-

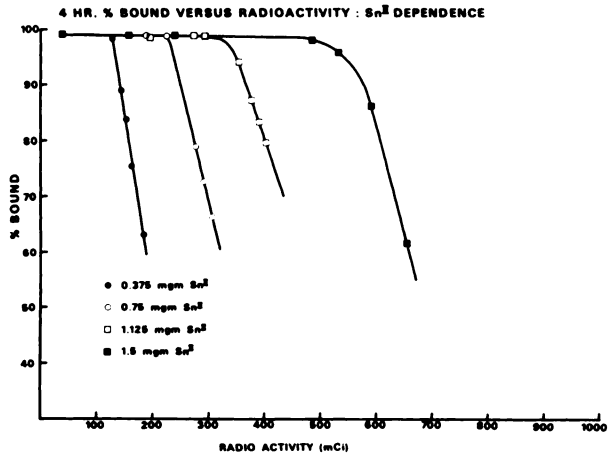

FIG. 6. Percentage of Tc-99m bound to pyrophosphate at 4 hr, against initial level of radioactivity, shows stabilizing effect of higher concentrations of stannous ions. All preparations had greater than 98% bound immediately after preparation.

ion quantities of 1.5 mg, 1.125 mg, and 0.75 mg in Series B. The critical radioactivity is a nonlinear function of the quantity of stannous ion.

Effect of external irradiation by 140-keV photons. Note that this radiolytic decomposition is due primarily to the lower-energy emissions of technetium-99m rather than to 140 keV. Experiments were made with one-milliliter samples of technetium pyrophosphate of low radioactivity in a thin glass tube, immersed in 20 ml [^{99m}Tc] pertechnetate having activity as high as 2.5 Ci. Such tests showed absolutely no radiolytic decomposition (Billinghurst M.W., unpublished data) and in fact calculations based on spectral data (*9*) of the absorbed dose in a 20-ml tube contained in a Wheaton S-19D 30-ml multidose vial showed that the 140-keV gammas account for only about ¼ of the absorbed energy.

CONCLUSION

The results reported here show that the appearance of pertechnetate in a technetium radiopharmaceutical that previously did not contain any unbound technetium may be caused by the effects of absorbed radiation.

The following specific conclusions may be drawn:

1. If the total chemical content of technetium is maintained at a constant level while the radioactivity is varied, good 4-hr stability of the labeled product will be maintained up to a certain "critical radioactivity," above which the quantity of pertechnetate in the preparation after 4 hr increases rapidly with increasing radioactivity (Series A).
2. If the Tc-99m/Tc ratio is kept constant and no Tc-99 is added, the same pattern is observed, indicating that this pattern is not related to the addition of Tc-99 obtained from decayed elutions (Series B and C).
3. The critical radioactivity is a logarithmic function of the total technetium content (Series A, B, and C).
4. The radiation-induced decomposition is dose-rate dependent.
5. The radiation-induced decomposition is catalyzed by the presence of dissolved oxygen but does not require the oxygen.
6. The presence of excess stannous ion acts as an inhibitor of the radiation-induced decomposition.

Although the effects reported here may not affect small laboratories using kits to prepare their Tc-99m radiopharmaceuticals, the radioactivity levels involved are not beyond those that may be reached by some centralized radiopharmacies. In addition,

these effects represent a practical limitation on efforts to minimize the excess stannous ion used in technetium radiopharmaceuticals.

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