Decomposition of Tc-99m Pyrophosphate by Peroxides in Pertechnetate Used in Preparation

Margaret Der, James R. Ballinger, and Barry M. Bowen

Chedoke-McMaster Hospital, Hamilton, Ontario, Canada

We describe an investigation of the stability of Tc-99m pyrophosphate (Tc-99m PPi). We have shown that addition of exogenous hydrogen peroxide to Tc-99m PPi can initiate the oxidation of the complex, giving rise to 95% unbound pertechnetate. The presence of endogenous hydrogen peroxide in the sodium pertechnetate used in the preparation of Tc-99m PPi has been thought to influence its stability. We have prepared it using pertechnetate solutions of different specific activities. After preparation, an alumina column was used to detect free $^{99m}TcO_4^-$. The Tc-99m PPi and $Na^{99m}TcO_4$ solutions were then assayed by iodometric titration for hydrogen peroxide, which was detected in the pertechnetate solutions. The higher the specific activity of the solution used for the tracer preparation, the faster was the production of free pertechnetate.

J Nucl Med 22: 645–646, 1981

The radiochemical purity of Tc-99m pyrophosphate (Tc-99m PPi) is important in producing acceptable bone images. The shelf instability of this tracer may be related to the specific activity of the sodium pertechnetate used in preparation. Thornton et al. (*1*) proposed that autoradiolysis of pertechnetate produced free radicals (hydroperoxy and hydroxy) that could in turn form hydrogen peroxide. He detected hydrogen peroxide in the range of 2–5 μg/ml in the solutions of pertechnetate, with the amount of peroxide proportional to the activity of the solution. Billinghurst et al. (*2*) found that by maintaining a total chemical content of technetium while varying the radioactivity, an acceptable 4-hr stability of the labeled product is maintained up to a certain critical radioactivity, above which the quantity of free $^{99m}TcO_4^-$ in the solution increases rapidly with increasing radioactivity. In our laboratory we have observed that the addition of 30 μg hydrogen peroxide to Tc-99m PPi solutions is capable of breaking the Tc-pyrophosphate complex. From Thornton's (*1*) work, we expected a higher concentration $Na^{99m}TcO_4$ to produce a higher level of hydrogen peroxide. This paper describes experiments to determine whether the endogenous levels of hydrogen peroxide present in the $Na^{99m}TcO_4$ affect the stability of the Tc-99m PPi.

METHODS

Production of free $^{99m}TcO_4^-$ in Tc-99m pyrophosphate. The Tc-99m PPi for injection was prepared in a multidose vial containing 2 ml of sodium pyrophosphate (25 mg/ml) and 1 ml of $Na^{99m}TcO_4$. One milliliter of a freshly prepared $SnCl_2$ solution (2 mg/ml in 0.1 *N* HCl) was added and the vial was shaken vigorously. The volume of solution was adjusted to 7 ml with 0.9% NaCl. For this preparation, two specific activities of pertechnetate were used: one just as it came in the generator eluate (~200 mCi/ml), and the other diluted to 60 mCi/ml with 0.9% NaCl. Immediately after the preparation, a paper chromatogram was developed in 85% methanol to ensure that labeling was complete and that no unbound pertechnetate was present (*3,4*). At hourly intervals after preparation the amount of unbound $^{99m}TcO_4^-$ in the Tc-99m PPi solutions was determined with an alumina column. This consisted of a 5-ml disposable syringe barrel fitted with a glass-wool plug at the tip and filled with 2.5 g of powdered, 95% activated alumina. The column was washed with ~5 ml acetone before use, then the 0.15-ml sample to be tested was eluted with 10 ml of acetone. The activities of the eluate and column were measured with a dose calibrator, the ratio of eluate to total activity giving the percentage of unbound pertechnetate in the test sample.

Determination of hydrogen peroxide content. This was not done until the solution had decayed for 1 day, due to the high specific activity of the $Na^{99m}TcO_4$ used in the preparation. The assay procedure involved an iodometric titration using starch as indicator (*1,3,5*). One-milliliter samples were reacted with iodine in an acetic acid medium with a molybdenum catalyst. The solution was then titrated with sodium thiosulfate to a colorless endpoint. The detection limit of the assay was 0.10 μg/ml. Three determinations were made on each sample.

RESULTS AND DISCUSSION

The production of free $^{99m}TcO_4^-$ in the Tc-99m PPi is plotted

---

Received June 10, 1980; revision accepted Jan. 21, 1981.

For reprints contact: B. M. Bowen, M.Sc.Phm. Dept. of Nuclear Medicine, Chedoke-McMaster Hospital, P.O. Box 2000, Station A, Hamilton, Ontario, Canada L8N 3Z5.

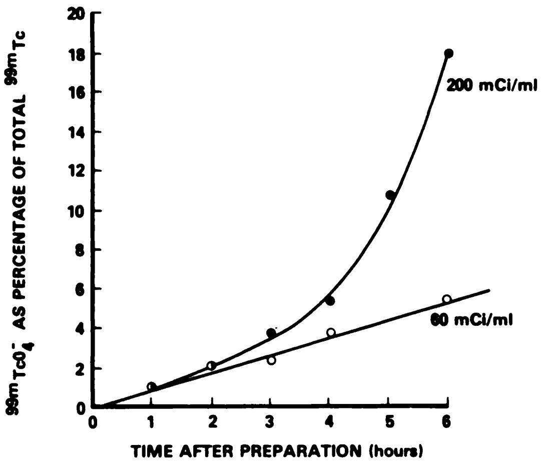

FIG. 1. Effect of specific activity of sodium pertechnetate solution on decomposition of Tc-99m PPi complex.

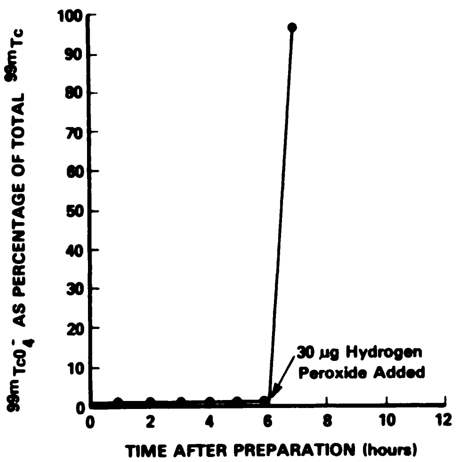

FIG. 2. Effect of addition of hydrogen peroxide to Tc-99m PPi complex.

in Fig. 1. The amounts present in the first 2 hr were identical for both Tc-99m PPi products. After 4 hr, however, the free pertechnetate was much greater for the tracer prepared with the higher $Na^{99m}TcO_4$ activity, exceeding the acceptable 5% level.

The addition of 30 µg of hydrogen peroxide to solutions of Tc-99m PPi that showed no evidence of free pertechnetate after 6 hr gave rise to 95% unbound pertechnetate within 15 min (Fig. 2). Thus the presence of hydrogen peroxide can initiate the oxidation of the complexed Tc-99m, although the exact concentration required to trigger the oxidation is not known.

Hydrogen peroxide is not the only possible agent responsible for the oxidation of the technetium in Tc-99m PPi; others include the free radicals hydroperoxyl (HOO$^\cdot$), and hydroxyl (HO$^\cdot$). Typically, these radicals are very reactive, unstable, and carry a large amount of energy. The combination of these radicals to form hydrogen peroxide is a favored reaction. Because of the reactivity, however, their direct measurement is very difficult, and we do not know the proportion of the oxidation due to the presence of hydrogen peroxide compared with that resulting from the hydroperoxyl and hydroxyl radicals.

The addition of an antioxidant is an effective method of stabilizing the Tc-99m PPi (*6*). Addition of 0.4 mg of L-cysteine to the tracer after preparation will result in less than 5% of unbound pertechnetate after 8 hr; it will protect the product against the addition of up to 30 µg exogenous hydrogen peroxide, this being much more than the levels of endogenous hydrogen peroxide reported by Thornton et al. (*1*).

Concentrations from 0.25–0.34 µg/ml of hydrogen peroxide were found in our $Na^{99m}TcO_4$ solution. We saw no relationship between specific activity of the generator eluate and the amount of hydrogen peroxide produced. We could detect none in the Tc-99m PPi; possibly because of interference by other substances, such as $SnCl_2$.

The oxidation of Tc-99m PPi cannot be explained solely by the activity of the $Na^{99m}TcO_4$ used in preparation, although this appears to affect shelf instability. Nevertheless, a low specific activity of $Na^{99m}TcO_4$ would ensure a longer shelf-life of the Tc-99m PPi.

REFERENCES

1. THORNTON AK, MOLINSKI VJ, SPENCER JT: Radiolytic prouduction of peroxides in technetium-99m solutions. *J Nucl Med* 20:653, 1979 (abst)

2. BILLINGHURST MW, REMPLE S, WESTENDORF BA: Radiation decomposition of technetium-99m radiopharmaceuticals. *J Nucl Med* 20:138–143, 1979

3. GOULD ES: *Mechanism and Structure in Organic Chemistry.* New York, Holt, Rinehart and Winston, 1960, p 693

4. ECKELMAN WC, RICHARDS P: Analytical pitfalls with ^{99m}Tc-labeled compounds. *J Nucl Med* 13:202–204, 1972

5. CHRISTIAN GD: *Analytical Chemistry.* 2nd ed. New York, John Wiley and Sons, 1975, p 325

6. TOFE AJ, BEVAN JA, FAWZI MB, et al: Antioxidant stabilization of bone agents. In *Radiopharmaceuticals II: Proceedings of 2nd International Symposium on Radiopharmaceuticals.* New York, Society of Nuclear Medicine, 1979, pp 637–644