

Technetium-99 in Generator Systems

Philip W. Moore

Australian Atomic Energy Commission Research Establishment, Lucas Heights Research Laboratories

Technetium-99m solutions always contain Tc-99. The amount varies considerably, depending on production methods and conditions, generator performance, and the time between production or separation and use. There is increasing evidence that labeling and imaging with some radiopharmaceutical kits is adversely affected when the Tc-99 exceeds certain amounts. The sensitivity of particular kits to Tc-99 depends on the ligand, the amount of usable Sn^{2+} , and the ratio of Tc to ligand. Although Tc-99 formed during production is removed in the final steps of generator manufacture, some may appear in early extractions in the solvent extraction process. If elution or extraction efficiencies are high, any Tc-99 is reduced within about two elutions to an insignificant level that is maintained in subsequent elutions. If efficiencies are below about 40%, however, the ratio of Tc-99 to Tc-99m increases with each elution.

J Nucl Med 25: 499–502, 1984

Because of the branching decay of Mo-99, and the decay of Tc-99m by isomeric transition, Tc-99m is always accompanied by Tc-99. Although the activity of the Tc-99 is negligible compared with that of the Tc-99m, even when present in amounts that are ten or 100 times greater, the two isomers react in the same way with components of radiopharmaceutical kits. During the past 7 or 8 yr there have been reports (1–4) that the labeling and imaging of some radiopharmaceuticals are adversely affected when the total Tc exceeds certain amounts—i.e., when there is a high atomic ratio of Tc-99 to Tc-99m (hereafter called the 99/99m ratio). If the Tc content of a generator eluate is expressed in terms of the 99/99m ratio, the total Tc in a radiopharmaceutical prepared from the eluate is

$$\text{Tc}(\text{ng}) = 5.14 (1 + 99/99\text{m}) \times \text{Tc-99m activity.}$$

Thus, the Tc content in SI units of ng/GBq is around five or six times the 99/99m ratio.

In 1975–76, Smith et al. (1,2) reported that when the Tc exceeded 1.48×10^{14} atoms (24 ng), the labeling efficiency of red blood cell (RBC) kits containing 1 μg of tin (Sn^{2+}) was decreased. Since 1 GBq of pure Tc-99m weighs 5.14 ng, the labeling efficiency in a test involving 1 GBq of activity is affected when the 99/99m ratio exceeds 4:1. These authors found that because various factors

decrease the amounts of available Sn^{2+} inside the RBCs, the capacity of the kits was insufficient to reduce all the Tc in some generator eluates and in most of the “instant” Tc solutions tested. They showed also that RBCs have limited capacity for Sn^{2+} , hence the use of larger amounts causes significant reduction of TcO_4^- outside the cells and, consequently, low labeling efficiency.

In 1976, Porter et al. (3) reported that the radiochemical purity fell below 90% when more than 3×10^{15} atoms of Tc was added to a human serum albumin kit. Subsequently, Srivastava et al. (4) reported sharply reduced labeling yields with some commercial DTPA lung agents when the number of Tc atoms added to the kits exceeded certain values. The labeling yield fell sharply in one case above 6×10^{14} atoms (100 ng), and in another, above 2×10^{16} atoms (3 μg).

Srivastava et al. also monitored several months' production of instant pertechnetate from four suppliers. Technetium levels varied from 76 to 2680 ng Tc/GBq (99/99m = 14 to 520) in a manner characteristic of the particular source (i.e., they were related to manufacturing conditions). Amounts frequently exceeded the reducing capacity of the usable Sn^{2+} in several commercial radiopharmaceutical kits. In another study, Mattsson (5) found Tc concentrations in instant pertechnetate equivalent to 78 to 7840 ng/GBq (99/99m = 14 to 1520). These results of Srivastava et al. and Mattsson were obtained by beta counting, and may be affected by traces of beta-emitting impurities in the pertechnetate.

More recently Deutsch et al. (6) and Bonnyman (7) have used high performance liquid chromatography (HPLC) to measure Tc-99 levels. Deutsch et al. reported amounts in generator eluates ranging from 8 to 95 ng/GBq (99/99m = 1 to 17) at elution.

Received Aug. 10, 1983; revision accepted Nov. 3, 1983.

For reprints contact: Philip W. Moore, PhD, Isotope Division, Australian Atomic Energy Commission Research Establishment, Lucas Heights Research Laboratories, Private Mail Bag, Sutherland, NSW, 2232, Australia.

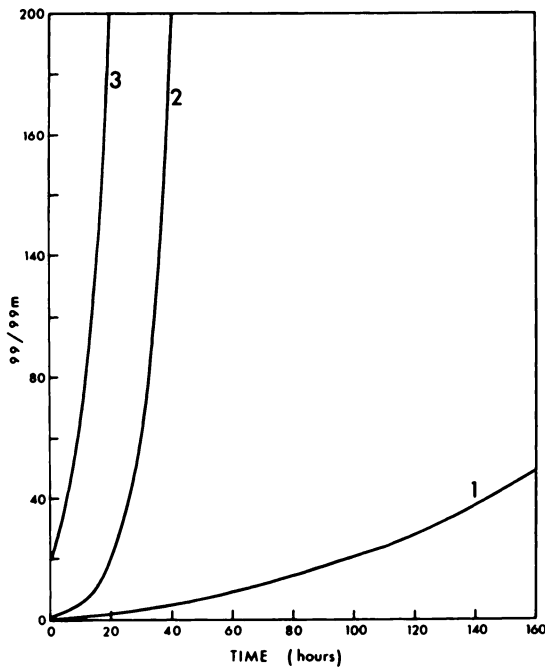


FIG. 1. Increase in 99/99m ratio in generator and eluates with time. Curve 1: 99/99m ratio in generator before elution (initial ratio \sim zero). Curve 2: 99/99m ratio in pertechnetate after elution. Curve 3: 99/99m ratio in pertechnetate after elution.

Bonnyman found amounts in first eluates from ten generators ranging from 95 to 1240 ng/GBq (99/99m = 17 to 240) at elution. He also found amounts in 36 instant pertechnetate samples ranging from 92 to 1280 ng/GBq (99/99m = 17 to 267, mean 368 ng/GBq) at use, corresponding to 11 to 176 ng/GBq (99/99m = 1 to 33) at extraction.

The work of Pinkerton et al. (8) and Deutsch et al. (6,9) may provide an explanation for differences in performance. Analysis by HPLC has shown (10-13) that many radiopharmaceuticals are mixtures of several complexes having different biodistributions. Higher concentrations of Tc favor second-order reactions and give rise to a wider range of oligomers and polymers that may differ in their proportions of Tc(IV), Sn(IV), and ligand. Thus, the poorer imaging obtained with higher concentrations of Tc could be due to the formation of different complexes or the same complexes in different proportions. The extent to which observed differences in imaging can be attributed to this cause is unknown at present.

If the presence of Tc-99 in pertechnetate is more important than has hitherto been realized, some knowledge is required of the amount of the Tc-99 isomer that can be expected under particular conditions of use. This paper brings to the attention of the technetium user the main factors affecting the amount of Tc-99 in pertechnetate solutions. A detailed mathematical treatment of the problem has been published elsewhere (14).

Production of Mo-99. The parent nuclide, Mo-99, is produced in a reactor either by the fission of uranium-235 or by the neutron activation of natural molybdenum. Since the nuclear reactions involving the formation and decay of Tc-99 and Tc-99m are independent of those producing the Mo-99, the 99/99m ratio in the irradiation target depends only on the length of the irradiation. For both methods, practical considerations usually limit the irradiation time to two or three product half-lives, i.e., \sim 7 days. Under these conditions, about 53% of the Mo-99, and more than 92% of the Tc-99m, decay before the irradiation is complete. At the end of a 7-day irradiation, the 99/99m ratio in the irradiation target is

about 14:1. Depending on the nature of subsequent processing, this may or may not influence the 99/99m in the first elution or extraction.

The Tc-99 formed in the reactor is of no consequence in the case of the uranium fission-product process because the Mo-99 is subsequently separated from the other products, including the Tc. Also, the Tc-99 formed by decay of Mo-99 and Tc-99m during processing can be ignored because it should be removed in a final washing operation during generator manufacture. However, the Tc-99 formed between the time the generator is assembled and the first elution—often 3 or 4 days,—can produce significant levels of Tc-99 in the first elution (Curve 1, Fig. 1).

The solvent extraction method. In this process, used to produce pertechnetate from irradiated molybdenum, the Tc-99 formed in the reactor, and during processing, appears in the first extraction. However, because the product from the first extraction may be contaminated with the activation products of trace impurities, it is usually discarded. Even so, experience has shown that unless particular attention is paid to the extraction conditions, extraction efficiencies can easily fall below 50%. Under these conditions some Tc-99m formed in the reactor will appear in decreasing amounts in the first few extractions.

Effect of elution or extraction conditions on the 99/99m ratio in eluates and extracts. If it is assumed that the two Tc isomers are eluted in the proportions in which they are present (i.e., that they are either both in an elutable chemical form, or that isotopic exchange can freely occur) the following information is obtained by an analysis of elution conditions (see Figs. 2 and 3):

1. Usually more than half the Tc-99m formed between elutions decays to Tc-99 before it is eluted.
2. The proportion that decays is greater for low elution efficiencies and for long intervals between elutions.
3. The 99/99m ratio decreases more rapidly when generators are eluted with high efficiency. With an elution efficiency of 90%, the ratio can be reduced from 20:1 to 4:1 in two elutions, 24 hr apart. By contrast, if the elution intervals are 24 hr and the efficiency is less than 40%, the 99/99m ratio will increase with each elution.
4. After a few elutions, the 99/99m ratio approaches a

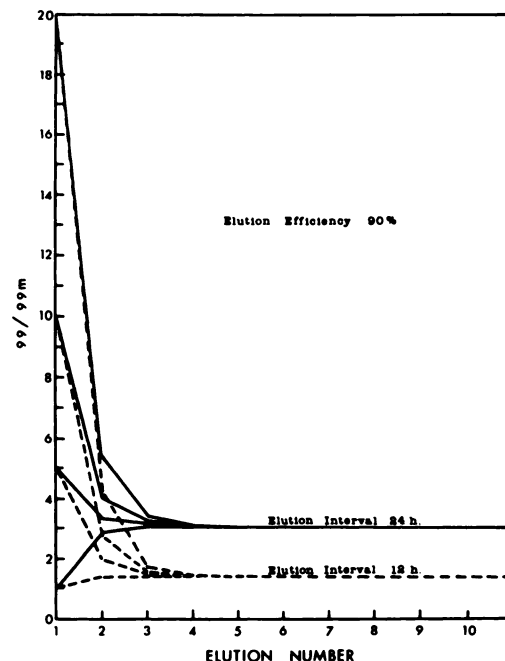


FIG. 2. Change in 99/99m ratio in successive elutions for selected ratios in first elution.

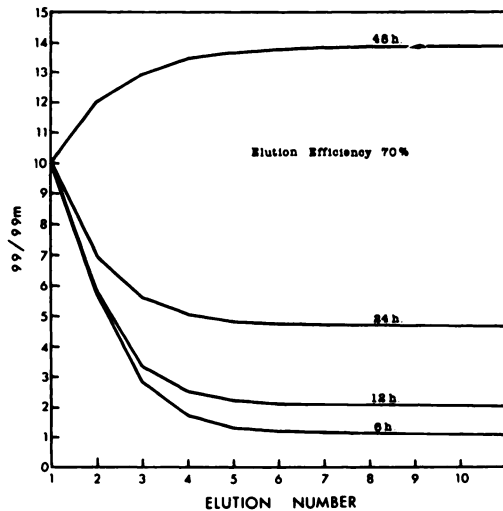


FIG. 3. Change in 99/99m ratio in successive elutions for different elution intervals.

steady-state value that depends upon the elution efficiency and the elution interval, and is independent of the initial ratio.

5. The steady-state ratio is less for high elution efficiencies and short elution intervals.

6. The steady-state ratio is reached earlier when the elution efficiency is high.

7. The time taken to reach the steady-state ratio is directly proportional to the elution interval.

Decay of Tc-99m after elution or extraction. The 99/99m ratio in separated pertechnetate increases faster than in the generator because the Tc-99m lost by radioactive decay is no longer replaced

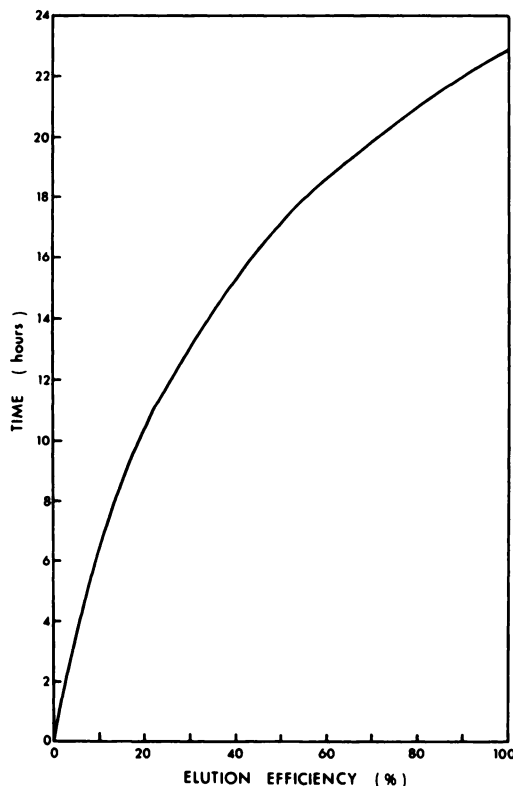


FIG. 4. Time required for generators to reach maximum activity following elution with stated efficiency.

by growth from Mo-99 decay (Fig. 1). If the ratio at elution is low, it remains at acceptable levels for 20 hr or more, and the useful life of the solution is determined more by the decline in Tc-99m activity than by the increase in the Tc-99 content. If the initial ratio is above about 20:1 at elution, it will climb in less than 20 hr to a level that could lead to poor labeling with some radiopharmaceutical kits. A comparison of Curves 2 and 3 in Fig. 1 shows the importance of low 99/99m ratios at elution.

Choosing a better elution regime. For convenience, generators are often eluted or extracted at 24-hr intervals, which is not the optimum frequency for obtaining either maximum Tc-99m activity or minimum Tc-99 content. If a generator is eluted with 100% efficiency, the maximum activity at the next elution is attained after a growth time of 22.9 hr, but if the efficiency is less than 100%, the maximum activity is reached in a shorter time. Thus, if the efficiency is 70%, the maximum yield of Tc-99m is obtained after 19.5 hr of growth, and if it is 50%, the maximum yield is obtained after only 17.1 hr (Fig. 4).

Accordingly it is suggested that if Tc-99 proves to be a problem, it can be reduced by eluting the generator at the start of a shift and washing it about 6 hr later. In this way a 24-hr cycle is maintained and the Tc-99 can be kept low with little or no sacrifice in activity. The procedure is most useful when the elution/extraction efficiency is low (Fig. 5).

Production methods and the importance of timing. Under typical production conditions, the solvent extraction method gives higher ratios than other methods, primarily because extraction efficiencies are lower. Levels of Tc-99 can increase to high values if the time between elution and use approaches 24 hr. With instant pertechnetate solutions, therefore, attention should be given to delivery times in order to obtain satisfactory 99/99m ratios at the time of use.

With portable chromatographic generators, the time between the final production wash and the first elution is critical. Because hospitals demand early delivery of generators, or because of international delivery schedules, this may exceed 90 hr and result in high 99/99m ratios in the first elution. However, because of the shorter time between elution and use, the ratio is not likely to reach the very high values possible with instant pertechnetate. Also, because of the usual high efficiency of chromatographic generators, the ratio can be expected to decrease considerably after the first one or two elutions.

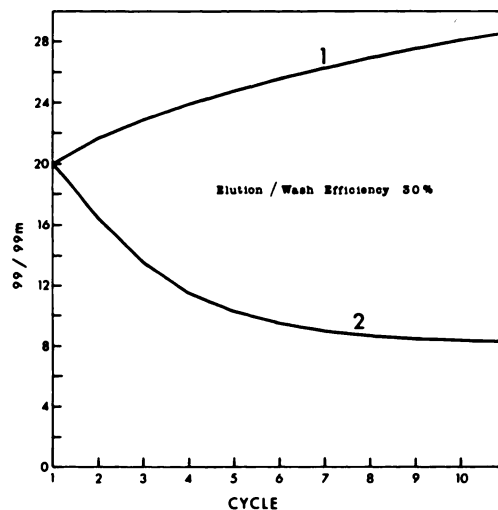


FIG. 5. Change in 99/99m ratio in successive elutions for two variations of 24-hr elution cycle. Curve 1: generator not washed between elutions. Curve 2: generator washed 6 hr after each elution.

If it is not possible to reduce the time between manufacture and use, and if the buildup of Tc-99 during transport affects the performance of the first eluate, the Tc-99 can be decreased by washing the generator 18 to 24 hr before the first elution. If, for example, a generator having a 99/99m ratio of 20:1 at 9 a.m. on Sunday is washed at that time with an efficiency of 90%, the 99/99m ratio in the first elution at 9 a.m. on Monday is 5:1 instead of 28:1. Although the wash decreases the 99/99m ratio by 81%, it reduces the Tc-99m activity in the first elution by only 7.5%.

CONCLUSION

Present practices, which are determined largely by the exigencies of production, transport, and clinical schedules, are influenced little, if at all, by consideration of their effects on Tc-99 levels. If further experience confirms indications that high Tc-99 levels can have an adverse effect on labeling and imaging, some practices may need revision, with more attention given to timing and to the efficiency and frequency with which generators are eluted or extracted.

REFERENCES

1. SMITH TD, STEIMERS JR, RICHARDS P: Chemical effect of Tc-99 on Tc-99m labeled radiopharmaceuticals. *J Nucl Med* 16:570-571, 1975
2. SMITH TD, RICHARDS P: A simple kit for the preparation of ^{99m}Tc-labeled red blood cells. *J Nucl Med* 17:126-132, 1976
3. PORTER WC, DWORKIN HJ, GUTKOWSKI RF: The effect of carrier technetium in the preparation of ^{99m}Tc-human serum albumin. *J Nucl Med* 17:704-706, 1976
4. SRIVASTAVA SC, MEINKEN G, SMITH TD, et al: Problems associated with stannous ^{99m}Tc-radiopharmaceuticals. *Int J Appl Radiat Isot* 28:83-95, 1977
5. MATTSSON S: Technetium-99 in "instant" ^{99m}Tc-per-technetate. *J Radioanal Chem* 45:341-347, 1978
6. DEUTSCH E, HEINEMAN WR, ZODDA JP, et al: Preparation of "no carrier-added" technetium-99m complexes: determination of the total technetium content of generator eluents. *Int J Appl Radiat Isot* 33:843-848, 1982
7. BONNYMAN J: Effect of milking efficiency on ⁹⁹Tc content of ^{99m}Tc derived from ^{99m}Tc generators. *Int J Appl Radiat Isot* 34:901-906, 1983
8. PINKERTON TC, FERGUSON DL, DEUTSCH E, et al: In vivo distributions of some component fractions of Tc (NaBH₄)-HEDP mixtures separated by anion exchange high performance liquid chromatography. *Int J Appl Radiat Isot* 33:907-915, 1982
9. DEUTSCH E, LIBSON K, JURISSON S, et al: Technetium chemistry and technetium radiopharmaceuticals. In *Progress in Inorganic Chemistry*, Vol. 30, New York, John Wiley and Sons, 1983, pp 75-139
10. PINKERTON TC, HEINEMAN WR, DEUTSCH E: Separation of technetium hydroxyethylidene diphosphonate complexes by anion-exchange high performance liquid chromatography. *Anal Chem* 52:1106-1110, 1980
11. FRITZBERG AR, LEWIS D: HPLC analysis of Tc-99m iminodiacetate hepatobiliary agents and a question of multiple peaks: Concise communication. *J Nucl Med* 21:1180-1184, 1980
12. NUNN AD, SCHRAMM E: Analysis of Tc-HIDAs and factors affecting their labeling rate, purity and stability. *J Nucl Med* 22:P52, 1981 (abst)
13. SRIVASTAVA SC, BANDYOPADHYAY D, MEINKEN G, et al: Characterization of Tc-99m bone agents (MDP, EHDP) by reverse phase and ion exchange high performance liquid chromatography. *J Nucl Med* 22:P69-P70, 1981 (abst)
14. MOORE PW: Technetium-99 levels in pertechnetate solutions from (n,γ) and (n,f) molybdenum-99 generators. *AAEC/ E565*, 1983

Education and Research Foundation Fundraiser Third Annual Tennis Tournament

June 4, 6, 7, 1984

L.A. Racquet Club

Los Angeles, California

The Education and Research Foundation Fundraiser Third Annual Tennis Tournament will be held June 4, 6, 7, 1984 at the L.A. Racquet Club, Los Angeles, California.

Organizers: Ben Greenspan, M.D.
Robert O'Mara, M.D.
Justine J. Parker

Court Time: Monday, June 4th
Wednesday, June 6th
Thursday, June 7th

Fee: \$15/person/day

Everyone is cordially invited to participate in this year's tennis activities. All proceeds from the tournament will be donated to the SNM Education and Research Foundation. To reserve your game, please write or call Jean Parker, P.O. Box 40279, San Francisco, CA 94140. Tel: (415)647-0722 or 647-1668. A check for \$5 (per person) payable to Western Region, SNM, must accompany your reservation.