Technetium-99m Radiopharmaceutical Preparation Problems: 12 Years of Experience

James A. Ponto

Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City; and College of Pharmacy, University of Iowa, Iowa City, Iowa

Objective: Chemical reactions involved in preparing ^{99m}Tc radiopharmaceuticals occasionally result in products of substandard purity. A retrospective examination of preparation problems that occurred in the author's institution was conducted to better define the incidence, recognize patterns and identify causes of substandard ^{99m}Tc radiopharmaceutical products.

Methods: All ^{99m}Tc radiopharmaceutical preparation and quality control testing records for the years 1986-1997 were reviewed, and preparation factors associated with substandard products were identified and examined.

Results: Fifty of 20,972 (0.2%) ^{99m}Tc products had substandard radiochemical purity; none were administered to patients. Twenty-eight of the 50 substandard products (56%) involved macroaggregated albumin with the remainder divided among in vitro red blood cells, exametazime, disofenin, sestamibi, mertiatide and sulfur colloid. Thirty-three of the 50 (66%) involved ^{99m}Tc-pertechnetate obtained as the first elution of a new generator and/or ^{99m}Tc-pertechnetate more than 12 hr old. Several of the substandard products involved other preparation factors and/or human error.

Conclusion: The majority of substandard ^{99m}Tc radiopharmaceutical products involved the use of ^{99m}Tc-pertechnetate containing excessive amounts of ^{99}Tc and/or oxidizing impurities to prepare products containing relatively small amounts of stannous. Although substandard products are an infrequent occurrence, radiochemical purity testing should be performed routinely on all ^{99m}Tc radiopharmaceuticals before patient administration.

Key Words: technetium-99m radiopharmaceuticals; preparation problems; radiochemical purity testing; quality control

J Nucl Med Technol 1998; 26:262–264

Unlike reconstituting or compounding conventional drugs, preparing ^{99m}Tc radiopharmaceuticals involves chemical reactions. Hence, a wide variety of problems may occur, the majority of which are related to substandard radiochemical purity (*1–4*). While a few of these preparation problems have been studied systematically in the laboratory, most are relatively infrequent in actual practice (*5*) and generally are mentioned only in case reports and abstracts. A retrospective examination of preparation problems that occurred in the author's institution was conducted to better define the incidence, recognize patterns and identify the causes of substandard ^{99m}Tc radiopharmaceutical products.

MATERIALS AND METHODS

All ^{99m}Tc radiopharmaceutical preparation and quality control testing records for the years 1986-1997 were reviewed. Substandard purity was defined as failure to meet radiochemical purity specifications in respective USP monographs (*6*). Technetium-99m radiopharmaceutical products exhibiting substandard radiochemical purity at the time of preparation were identified and factors associated with their preparation were examined.

RESULTS

Of the 20,972 ^{99m}Tc radiopharmaceuticals that were prepared, 50 products (0.2%) were of substandard purity. Macroaggregated albumin was involved in 28 (56%) of the substandard products. Other substandard products included in vitro red blood cells, exametazime, disofenin, sestamibi, mertiatide and sulfur colloid. Thirty-three (66%) of the substandard products were prepared using ^{99m}Tc-pertechnetate obtained as the first elution of a new generator and/or ^{99m}Tc-pertechnetate more than 12 hr old. Other preparation factors resulting in substandard quality, such as inadequate heating or improper mixing order, also were identified. These data are detailed in Table 1. None of these substandard products was administered to patients.

DISCUSSION

Preparation of ^{99m}Tc radiopharmaceuticals, although technically simple, involves chemical reactions that occasionally are

For correspondence or reprints contact: James A. Ponto, MS, RPh, BCNP, Nuclear Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Dr., Iowa City, IA 52242.

TABLE 1
Numbers of Substandard Technetium-99m-Pertechnetate Radiopharmaceutical Products

Product	First elution of a new generator	^{99m}Tc-pertechnetate >12 hr old	Both first elution and >12 hr old	Other	Subtotal	Percent total
MAA	9	9	8	1 Defective vial (no particles) 1 ^{99m}Tc-pertechnetate > 8 hr old	28	56%
RBCs	1	1	3	1 Wrong mixing order (syringes reversed) 1 Excess reaction volume (4 ml ^{99m}Tc-pertechnetate) 1 Unknown	8	16%
HMPAO	—	—	—	1 ^{99m}Tc-pertechnetate > 6 hr old 4 Unknown (first few lots after NDA)	5	10%
DISIDA	1	1	—	1 Unknown	3	6%
MIBI	—	—	—	2 Inadequate heating 1 Delay > 10 min before heating	3	6%
MAG3	—	—	—	2 Inadequate heating	2	4%
SC	—	—	—	1 Wrong mixing order (syringes reversed)	1	2%

MAA = macroaggregated albumin; RBCs = in vitro red blood cells; HMPAO = exametazime; DISIDA = disofenin; MIBI = sestamibi; MAG3 = mertiatide; SC = sulfur colloid.

problematic, resulting in products with substandard radiochemical purity. Administration to patients of such substandard products would manifest as altered biodistribution and could interfere with diagnostic interpretation (*1–4*). Moreover, these patients would receive unnecessary radiation doses if suboptimal images necessitated repetition of the procedures (*7*). Hence, quality control testing of radiochemical purity should be performed routinely on each ^{99m}Tc radiopharmaceutical product before dispensing (*1–4,7*).

Despite the myriad potential preparation problems, substandard ^{99m}Tc radiopharmaceutical products are encountered infrequently in actual practice. The incidence of substandard products observed in this study, 0.2%, is similar to that previously reported, 0.2%–0.8%, in a sample of diverse nuclear pharmacy settings (*5*). Even at these low rates of preparation problems, routine quality control testing of radiochemical purity before patient administration has been shown to be cost effective (*5*).

The majority of preparation problems observed in this study involved macroaggregated albumin products. Among radiopharmaceuticals, macroaggregated albumin kits contain relatively small amounts of stannous as a reducing agent. Inadequate reducing capacity is one of the more common preparation problems that results in substandard ^{99m}Tc radiopharmaceutical products (*1–4*). Several preparation problems involving in vitro red blood cells and exametazime kits, which also contain relatively small amounts of stannous, were observed also.

The majority of the substandard products observed in this study were prepared using ^{99m}Tc-pertechnetate obtained as the first elution of a new generator and/or ^{99m}Tc-pertechnetate more than 12 hr old. In these situations, more than the usual amounts of carrier ^{99}Tc (resulting from the decay of ^{99m}Tc) build up in the ^{99m}Tc-pertechnetate solution (*8*) and competitively interfere with the reduction and chelation reactions necessary in preparing most ^{99m}Tc radiopharmaceuticals (*1–4*). Moreover, radiolytic ionization of water in generators and ^{99m}Tc-pertechnetate solutions produces hydrogen peroxide and hydroperoxy free radicals which readily oxidize stannous (*9,10*). This decrease in reducing capacity, especially in combination with increased competition from ^{99}Tc, is one of the more common preparation problems that results in substandard ^{99m}Tc radiopharmaceutical products (*1–4*).

The use of ^{99m}Tc-pertechnetate obtained as the first elution of a new generator and/or ^{99m}Tc-pertechnetate more than 12 hr old does not result consistently in a substandard product. In fact, products of high quality are frequently prepared using these types of ^{99m}Tc-pertechnetate (*5*). On the other hand, the use of ^{99m}Tc-pertechnetate that is as little as 2 hr old can result in substandard quality for some products such as exametazime (*1–4*). Hence, other factors, including variation in storage conditions, trace contaminants from containers and closures, and intra- and interlot variability, play important, albeit poorly-defined, roles in affecting radiochemical purity (*1–4*).

Other preparation problems observed in this study are detailed in Table 1. Although several occurrences remain unexplained, most substandard products involved preparation factors or conditions that have been identified previously as problematic (*1–4*). A few of these, such as improper mixing order and inadequate heating, resulted from human error or inattention to written procedures.

CONCLUSION

The majority of substandard ^{99m}Tc radiopharmaceutical products involved the use of ^{99m}Tc-pertechnetate containing excessive amounts of ^{99}Tc and/or oxidizing impurities to prepare products containing relatively small amounts of stannous. Several other preparation factors and human error also were involved in causing products to be of substandard quality. Although substandard products are an infrequent occurrence, radiochemical purity testing should be performed routinely on all ^{99m}Tc radiopharmaceuticals before patient administration.

REFERENCES

1. Ponto JA, Swanson DP, Freitas JE. Clinical manifestations of radiopharmaceutical formulation problems. In: Hladik WB, Saha GB, Study KT, eds. *Essentials of nuclear medicine science*. Baltimore:Williams & Wilkins;1987: 268–289.
2. Ponto JA. A review of radiopharmaceutical formulation problems and their clinical manifestations. In: Hladik WB, ed. *Correspondence continuing education courses for nuclear pharmacists and nuclear medicine professionals*, vol. II, no. 3. Albuquerque:University of New Mexico;1993:1–45.
3. Hojelse C, Kristensen K, Sampson CB. Factors which affect the integrity of radiopharmaceuticals. In: Sampson CB, ed. *Textbook of radiopharmacy–theory and practice*. 2nd ed. Langhorne, PA:Gordon and Breach Science Publishers;1994:145–151.
4. Hung JC, Ponto JA, Hammes RJ. Radiopharmaceutical-related pitfalls and artifacts. *Semin Nucl Med* 1996;26:208–255.
5. Ponto JA, Ponto LL. Cost-effectiveness of routine radiochemical quality assurance testing of technetium Tc-99m radiopharmaceuticals. *Am J Hosp Pharm* 1986;43:1218–1222.
6. Committee of Revision. *The United States Pharmacopeia USP 23/The National Formulary NF 18*. Rockville, MD:United States Pharmacopeial Convention, Inc.;1994.
7. Eckelman WC, Herrara NE, Hauser W. Radiopharmaceutical quality assurance—pilot study [Letter to Ed]. *J Nucl Med* 1981;22:94.
8. Lamson ML, Kirschner AS, Hotte CE, Lipsitz EL, Ice RD. Generator-produced $^{99m}TcO_4^-$, carrier-free? *J Nucl Med* 1975;16:639–641.
9. Colombetti LG, Barnes WE. Effect of chemical and radiochemical impurities from eluants on ^{99m}Tc-labeling efficiency. *Nuklearmedizin* 1977;16:271–274.
10. Molinski VJ. A review of ^{99m}Tc generator technology. *Int J Appl Radiat Isot* 1982;33:811–819.