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The Tc-99m Supply Shortage: Impact on Nuclear Labs

INTRODUCTION

News of a possible disruption in the global technetium-99m (Tc-99m) supply was first made public on May 18, 2009, when the Atomic Energy of Canada Limited (AECL) announced that the National Research Universal (NRU) reactor in Chalk River, Ontario, had to be shut down unexpectedly due to a heavy water leak discovered during routine monitoring.[1] The NRU reactor produces 30%-40% of the world's medical isotopes and approximately 50% of those used in North America.[2] As 1 of only 4 reactors in the world with the capacity to produce significant commercial quantities of molybdenum-99 (Mo-99), which is used in the manufacturing of Tc-99m, it was expected that a significant shortage in Tc-99m would be felt worldwide.[2]

This Special Bulletin contains background information on the radiopharmaceuticals used in single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), as well as an accounting of the Tc-99m shortage, its impact on the practice of nuclear cardiology, and strategies to ensure the optimal use of available Tc-99m supplies. The information in this Bulletin is current as of the end of 2009, and readers are encouraged to stay informed about the latest developments by visiting several Web sites that post updates on the Tc-99m supply shortage, listed at the end of this Special Bulletin.

Table 1. **Radiopharmaceuticals used in SPECT MPI[3,4]**

	Tl-201	Tc-99m Sestamibi	Tc-99m Tetrofosmin
Dose for MPI, mCi[3]	1.0-4.0	2.5-36	2.5-36
Preparation[5]	Cyclotron	Kit	Kit
Half-life, hours[3]	73.1 hours	6	6
First-pass extraction	85%[3]	55%[6]	54%[7]
Redistribution[5]	Yes	Negligible	Negligible
Time to SPECT image acquisition, minutes[3]	10-15 for stress (exercise or pharmacologic)	15-20 for exercise, 60 for pharmacologic stress	10-15 for exercise, 45 for pharmacologic stress
	Redistribution imaging 2.5-4.0 hours later	45-60 for rest	30-45 for rest

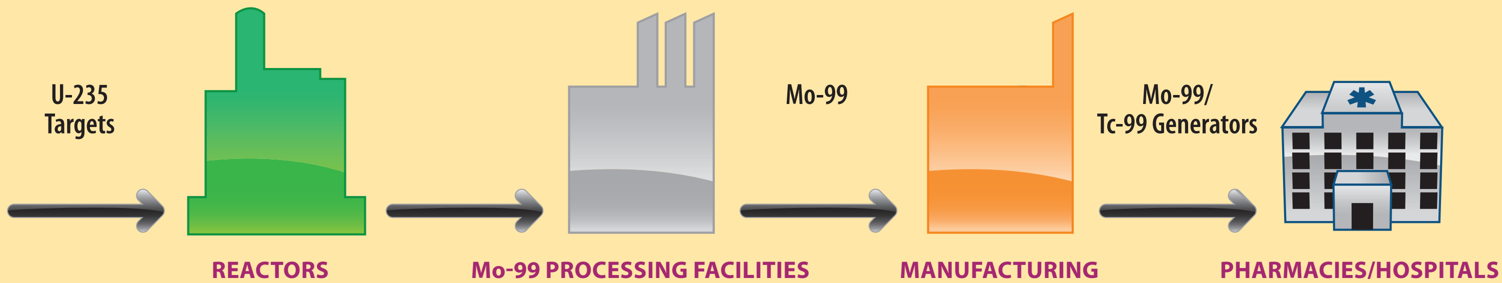
RADIOPHARMACEUTICALS IN MPI

There are 3 radiopharmaceuticals used in SPECT MPI in the US: thallium-201 (Tl-201), Tc-99m sestamibi, and Tc-99m tetrofosmin.[3,4] Each radiopharmaceutical has different myocardial extraction properties at rest and during stress, and different half-lives that dictate the dose, timing of injection, and image acquisition protocols used for SPECT MPI (Table 1).[3,4] The selection of a particular radiopharmaceutical is dependent on its diagnostic accuracy, as well as its ease of use and availability.[4,5]

THE TC-99M SUPPLY CHAIN

Tc-99m is used in approximately 80% of radiopharmaceuticals used in medical imaging, and the imaging tests that rely on Tc-99m, including SPECT MPI, are the most commonly used tests in nuclear medicine.[8] Tc-99m is a decay product of Mo-99.[9] The global Tc-99m supply chain begins with the production of Mo-99 from highly enriched uranium by 5 reactors located in The Netherlands, France, Belgium, Canada, and South Africa (Figure 1).[9] Mo-99 is then processed in 4 facilities in The Netherlands, Belgium, Canada, and South Africa.[9] Finally, Mo-99 is shipped to 5 generator facilities, 2 of which are located in the US, which manufacture Tc-99m generators for distribution to hospitals and pharmacies.[9] Routine reactor shutdown schedules are carefully coordinated between the 5 Mo-99 reactors in order to minimize disruption to the Tc-99m supply.[10] When Mo-99 reactors go offline due to unplanned safety issues, however, the entire supply chain can be disrupted and restrict the available supply of Tc-99m.

Figure 1. The Global Tc-99m Supply Chain[9]



Reactors

- Belgian Nuclear Radiopharmacy Centre (BR2), Belgium
- French Atomic Energy Commission (CEA), Centre at Saclay (Osiris), France
- National Research Universal Reactor (NRU), Canada
- Nuclear Research & Consultancy Group (NRG) (HFR), The Netherlands
- South African Nuclear Energy Corporation (NECSA) (Safari-1), South Africa[a]

Mo-99 Processing Facilities

- Covidien, The Netherlands
- MDS Nordion, Canada
- Nuclear Technology Products (NTP), South Africa
- The Institute for Radio Elements (IRE), Belgium

Manufacturing

- Covidien, Missouri, USA
- Covidien, Petten, The Netherlands
- GE Healthcare & Biosciences, United Kingdom
- Ion Beam Application (IBA SA) / CIS Bio International, France
- Lantheus Medical Imaging, Massachusetts, USA

Highly enriched uranium is used to produce Mo-99 in 5 reactors; the Mo-99 is processed in 4 processing facilities and then shipped to 5 Tc-99m generator manufacturing facilities, 2 of which are located in the US.[9]

[a] The NECSA Safari-1 reactor was converted to low-enriched uranium in June 2009.[11]

THE CURRENT TC-99M SHORTAGE

The latest Tc-99m shortage began with the shutdown of the Chalk River NRU reactor in Ontario, Canada, in May, which supplies about 60% of the US supply of Tc-99m.[12,13] After assessment of the extent of damage, the AECL estimated that the NRU will not return to service before early 2010.[12,14]

The potential effects of the NRU shutdown on the Tc-99m supply were compounded by the shutdown of the High Flux Reactor (HFR) in Petten, The Netherlands, for maintenance for a few days during the first week of June[15] and again in early July.[10] In addition, a third, previously scheduled shutdown of the HFR began on July 18, with a planned return to service on August 18.[16,17] With the Chalk River and Petten reactors supplying approximately 64% of the world's Mo-99, it was estimated that the global production of Mo-99 would be drastically reduced for at least 1 month.[13,18] A second scheduled maintenance outage of the HFR is set for approximately 6 months in 2010, which is expected to prolong the global Tc-99m shortage.[13]

STABILIZING THE US TC-99M SUPPLY

The timing of the reactor outages has revealed the volatility of the global Tc-99m tracer supply in the US. Domestic manufacturers of Tc-99m generators are trying to accommodate the NRU and HFR reactor shutdowns by diversifying their supply chain and increasing orders with other Mo-99 reactors, and by investing in their manufacturing facilities to maximize output of Tc-99m.[9,19,20]

Recognizing the impact of the latest tracer shortage on the practice of nuclear medicine in the US, tracer manufacturers,[9,19,21] professional societies, and government bodies have called for the development of a reliable domestic source of medical isotopes. In July, ASNC sent a letter to Congress urging them to include sufficient funding in the Energy and Water Development appropriations bill for production of medical isotopes in the US and to provide financial incentives to industry to expedite isotope production.[22]

Concurrently, Rep. Edward J. Markey (D-Mass.) and Rep. Fred Upton (R-Mich.) introduced H.R. 3276 The American Medical Isotopes Production Act 2009 to ensure a reliable domestic supply of medical isotopes.[13] The bill would authorize $163 million over 5 years for funding the Department of Energy to evaluate and support research and private sector projects that will establish Mo-99 production in the US.[23] The funded program would assist in the development of alternative processes that avoid the use of highly enriched uranium for producing commercial quantities of Mo-99.[23] Additionally, the bill proposes to phase out the export of highly enriched uranium over 7-10 years, providing sufficient time for alternative technologies (ie, use of low-enriched uranium) for producing Mo-99 to be implemented.[23] The legislation was endorsed by 14 professional societies, organizations, hospitals, and companies that have been impacted by the Mo-99 shortage, including the American College of Cardiology (ACC), ASNC, American College of Radiology (ACR), and the Society of Nuclear Medicine (SNM).[13] The presidents of ASNC and the ACC subsequently issued a statement applauding the legislative efforts.[24] The bill was submitted to the House Committee on Energy and Commerce for consideration,[25] and the Subcommittee on Energy and Environment held a legislative hearing on September 9, 2009.[26]

The FDA is also working with US manufacturers of Tc-99m generators to help increase production, as well as keeping health care providers informed of the situation via the CDER Drug Shortage Web site.[8]

STRATEGIES FOR COPING WITH THE TC-99M SHORTAGE

The impact of the tracer shortage is being felt widely within the nuclear cardiology community and is now affecting patient care. In a survey of more than 250 ASNC members conducted in August by the US Department of Energy, respondents indicated that they have decreased their standing orders of Tc-99m, and have deferred patients, changed the type of procedure performed, and substituted other radioisotopes due to the lack of Tc-99m.[27] Half of the respondents indicated that there have been weeks in which no Tc-99m was available and the average delay in receiving Tc-99m was nearly 6 days.[27]

Because the half-life of Mo-99 is 67 hours,[9] stockpiling the isotope is not possible, and health care providers must maximize use of available Tc-99m, prioritize SPECT MPI procedures that require Tc-99m, and consider alternative diagnostic procedures or protocols.[8] The FDA recommends taking into consideration the radioactive decay of Tc-99m when scheduling tests in order to use available supplies most efficiently.[8] Covidien recently announced a Tc-99m conservation policy that encourages labs to order doses closer to the time of the scheduled test, a "just in time" approach to reduce loss due to tracer decay.[28]

Some labs may try to optimize the use of their Tc-99m supply by performing stress Tl-201 or dual-tracer SPECT MPI protocols in place of Tc-99m-only protocols.[3] ***(Note: Before implementing alternative SPECT MPI protocols, it is important to make sure your lab is accredited to perform them.)*** Although performed rarely since the introduction of Tc-99m, some labs may re-institute stress Tl-201 protocols (Figure 2A).[3] Because higher energy imaging and the tracer distribution kinetics of Tc-99m decrease imaging artifacts caused by tissue attenuation,[3,4] Tl-201 protocols may be more appropriate for smaller patients or those with low pretest risk, with Tc-99m reserved for imaging larger patients or large-breasted women. Another option for reducing Tc-99m may be the dual-tracer protocol, which takes advantage of the unique uptake and distribution properties of each tracer during rest (Tl-201) and stress (Tc-99m).[3] The major disadvantage of this protocol is high radiation exposure, with patients potentially receiving 27.3 mSv per procedure (Figure 2B).[3,29]

Stress-only imaging may be another strategy for reducing Tc-99m use.[30,31] ASNC released a clinical update in 2009 approving the use of stress-only imaging protocols in certain patients (Figure 3).[32] In this strategy, patients with low pretest risk or who can exercise would undergo an initial stress SPECT MPI, and based on the stress images, a decision is made about whether to proceed with rest imaging.[30-32] If the stress images are normal, the patient would not need to undergo the rest portion of the test; however, if there is any abnormality on the stress images, or if other risk factors (eg, clinical risk factors, abnormal ECG) suggest the potential for coronary heart disease, the patient would undergo rest imaging.[32] A stress-only study can be carried out with or without attenuation correction, or by imaging patients supine and then prone with gating to ensure accurate images.[32] Stress-only imaging reduces the amount of radiopharmaceutical used, reduces patient and staff radiation exposure, reduces unnecessary rest scans in low-risk patients, and saves both time and healthcare costs.[32]

In certain centers, PET MPI may be an alternative to Tc-99m SPECT MPI during the tracer shortage.[33,34] PET MPI is performed at rest and during pharmacologic stress, most commonly with rubidium-82 (Rb-82) or N-13 ammonia.[4,33,34] The short half-lives of the PET tracers allow both rest and stress images to be acquired in 15 minutes to 1 hour (Figure 4).[33] PET can assess left ventricular function (with gating) as well as viability (with 18-fluorodeoxyglucose).[34] The major drawbacks to PET MPI are the high cost of the cameras compared with SPECT, the high cost of producing the radiopharmaceuticals, and the lack of reimbursement for cardiac PET procedures.

Figure 2A. Stress/redistribution/reinjection Tl-201 SPECT MPI protocol.[3]

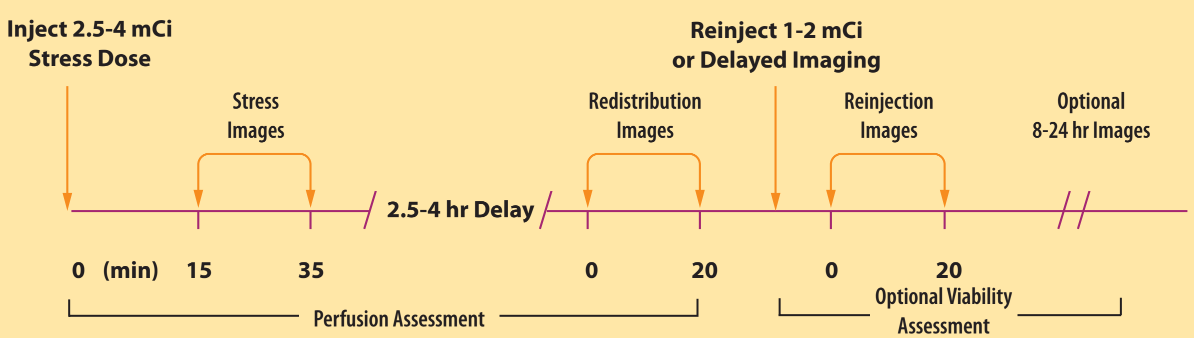


Figure 2B. Dual-tracer SPECT MPI protocol.[3]

[a] Timing of radiopharmaceutical injection during the stress portion of the protocol is dependent upon the type of stress used.[3]

Figure 3. Stress-only Tc-99m SPECT MPI strategy.[3,32]

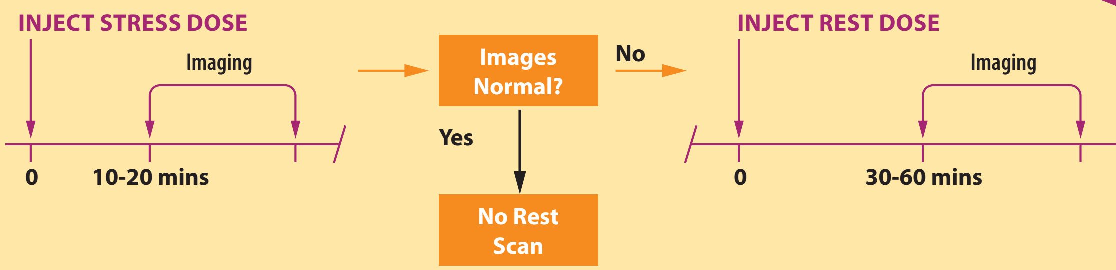
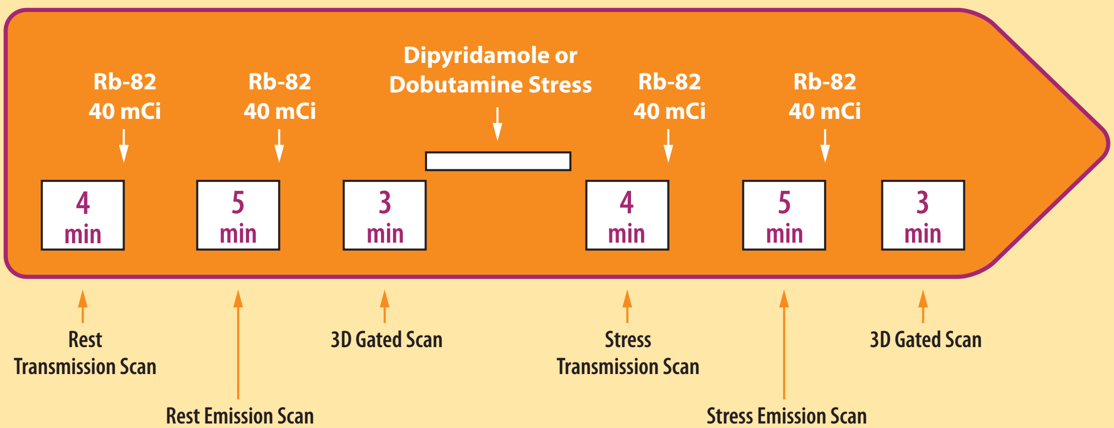


Figure 4. 60-minute PET MPI protocol.[33]



CONCLUSIONS

The current shortage in Tc-99m radiopharmaceuticals, which are used in the majority of SPECT MPI imaging procedures in the US, is a consequence of an unplanned shutdown of a major Mo-99 reactor in Canada that occurred at the same time as a scheduled maintenance shutdown of a second reactor in The Netherlands. The situation has revealed the need for a stable, domestic supply of medical radiopharmaceuticals, and legislation has been drafted in an attempt to address this issue. In the meantime, nuclear labs must find ways to maximize their current Tc-99m supplies and reduce their use of Tc-99m during the shortage. Creative scheduling, restricting the use of Tc-99m to certain patients, and use of alternative imaging protocols and strategies may be necessary until the global supply of Tc-99m stabilizes.

For continuing updates on the global Mo-99 shortage, please visit these sites:

ASNC – Information About Potential Disruption in Global Mo-99 Supply
http://www.asnc.org/content_7978.cfm

SNM – Domestic Isotope Availability
http://www.snm.org/index.cfm?PageID=7739&RPID=10

Covidien – Molybdenum 99 (Mo 99) Supply Update
http://www.covidien.com/Mo99supply

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