Potential ways to address shortage situations of Mo-99/Tc-99m

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ABSTRACT

Technetium 99m (Tc-99m) is the most common radioisotope used in nuclear medicine, which is produced in a nuclear reactor from the decay of molybdenum-99 (Mo-99). There are only a few aging nuclear reactors around the world that produce Mo-99 and one of the major contributors, the NRU (National Research Universal, Canada), will cease production on October 31, 2016. The NRU produces approximately 40% of the world's Mo-99 supply, so with its impending shut down, shortages of Mo-99/Tc-99m are expected. **Methods:** Nuclear pharmacies and nuclear medicine departments throughout the United States were contacted and asked to provide their strategies for coping with a shortage of Mo-99/Tc-99m. Each of these strategies was evaluated based on its effectiveness for conserving Tc-99m while still meeting the needs of the patients. **Results:** From the responses, six categories of strategies, in order of importance, were compiled: (1) contractual agreements with commercial nuclear pharmacies, (2) alternative imaging protocols, (3) changes in imaging schedules, (4) software utilization, (5) generator management, and (6) reducing ordered doses or eliminating "backup" doses. **Conclusion:** The supply chain of Mo-99/Tc99m is quite fragile; therefore, being aware of the most appropriate coping strategies is crucial. It is essential to build a strong collaboration between the nuclear pharmacy and nuclear medicine department during a shortage situation. With both nuclear medicine departments and nuclear pharmacies implementing viable strategies, such as the ones proposed, the amount of Tc-99m available during a shortage situation can be maximized.

Key Words: Mo-99, Tc-99m, radioisotope shortage, nuclear reactors, radioisotope productions.

INTRODUCTION

Technetium-99m (Tc-99m) is a principal radioisotope used for medical diagnostic imaging, and accounts for approximately 80-85% of all nuclear medicine procedures (*1*). Tc-99m is the daughter product of molybdenum-99 (Mo-99), and it is typically supplied in the form of a Mo-99/Tc-99m generator to make diagnostic radiopharmaceuticals.

The global supply chain of Mo-99 used for generator production has numerous complex problems, which makes the system fragile and unreliable. Limited suppliers, aging reactors, and transportation obstacles are all challenges faced with the supply chain (*2*). Mo-99 is exclusively produced in seven nuclear reactors with an average age of these reactors being >40 years old (*2*). These seven nuclear reactors are the Belgian Reactor 2 (BR-2) in Belgium, High Flux Reactor in the Netherlands, LVR-15 REZ Reactor in the Czech Republic, Maria Research Reactor in Poland, National Research Universal (NRU) in Canada, Open Pool Australian Lightwater reactor in Australia, and South African Fundamental Atomic Research Installation in South Africa (*2*). In recent history, these reactors have encountered unscheduled maintenance and refurbishment periods impacting the supply of Mo-99.

The seven nuclear reactors provide over 90% of the world's Mo-99 (*2*). Global shortages of Tc-99m emerged in 2009 due to two aging nuclear reactors (NRU in Canada and High Flux Reactor in the Netherlands) shutting down. Currently the OSIRIS (France) ceased production permanently. The BR-2 (Belgium) initiated a 12-month refurbishment early last year with another projected six months to complete the rebuild. The NRU will end its Mo-99 production on October 31, 2016 (*3*). Any Mo-99 production from the NRU after that date would be subject to the discretion of the Canadian government (*3*). It has been proposed to keep the NRU in "hot standby" until March 31, 2018 (*3*). The Canadian government has not released the decision-making process for restarting Mo-99 production from the NRU after it ceases routine Mo-99 production on October 31, 2016.

After being produced in nuclear reactors, Mo-99 is transferred to a processing facility to be chemically separated and purified. There are currently only five Mo-99 processing facilities in the world, which are Australian Nuclear Science and Technology Organisation (ANSTO) in Australia, The Institute for Radio Elements (IRE) in Belgium, Mallinckrodt in the Netherlands, Nordion in Canada, and Nuclear Technology Products (NTP) Radioisotopes SOC Ltd in South Africa (*2*). The finished Mo-99 product material is then isolated and shipped to one of eight generator manufacturing facilities which supply Mo-99 in the form of a Mo-99/Tc-99m generator to end users, such as nuclear pharmacies and hospitals (*2*). The eight generator manufacturing facilities are ANSTO (Australia), GE Healthcare (United Kingdom), IBA Molecular (France), Lantheus Medical Imaging (United States), Mallinckrodt (Netherlands and United States), Monrol (Turkey), National Centre for Nuclear Research (NCBJ) Radioisotope Centre POLATOM (Poland), and NTP Radioisotopes SOC Ltd in South Africa (*2,4)*.

In addition to the fragile reactor and Mo-99 processing facility infrastructures, the time frame to deliver purified Mo-99 to generator manufacturers is limited. Major transportation obstacles such as customs, government regulations, flight schedules, weather delays, pilot refusal, and natural disasters have the potential to result in significant product shipment delay (*2*).

It is difficult to predict when the next major Mo-99/Tc-99m shortage will take place. As such, it is important for each nuclear medicine facility to develop strategies in order to deal with periods of shortage. The purpose of this study was to identify potential approaches to manage shortage situations of Mo-99/Tc-99m.

MATERIALS AND METHODS

Strategies for managing Mo-99/Tc-99m in shortage situations were gathered and pooled from a variety of sources. First, research was performed to gain information about the Mo-99 supply chain. This included information about the seven nuclear reactors, the five processing facilities, the eight generator manufacturing facilities and the tight transportation obstacles, in order to understand the potential causes of shortages and to formulate applicable strategies to deal with these problems. A literature review was then executed to identify previous shortages, with the primary focus being the most recent global shortage in 2009-2010. The literature review concentrated on the global supply of Mo-99, and information was gained from the perspectives of the OECD Nuclear Energy Agency, The Nuclear Science Advisory Committee, nuclear pharmacies and hospitals (*3,5*). All of the articles used contained current information and were published within the last 3 years.

Next, nuclear medicine technologists and nuclear pharmacists employed at Mayo Clinic were interviewed. The purpose of these interviews was to obtain the approaches established by the Nuclear Medicine department at Mayo Clinic to cope with the 2009-2010-shortage crisis, and to evaluate their effectiveness. If a shortage were to occur again, would they react similarly or would new strategies be implemented?

Lastly, survey questionnaires and phone interviews were conducted with eight outside sources. This included supervisors at outside nuclear medicine departments, and nuclear pharmacists and managers at commercial nuclear pharmacies across the United States. Each outside source was asked to provide its “Top 3” coping strategies for a Mo-99/Tc-99m shortage. All the coping strategies were then compiled and evaluated based on effectiveness for procuring Tc-99m or conserving Tc-99m while still meeting the needs of the patients.

RESULTS

The viable responses were placed into six categories of coping strategies which include: (1) contractual agreements with commercial nuclear pharmacies (2) alternative imaging protocols, (3) changes in imaging schedules (4) software utilization, (5) generator management, and (6) reducing ordered doses or eliminating “backup” doses (Table 1). These responses are listed based on importance, with the most critical strategy first. They are also broad in terms for the nuclear medicine world and vary based on department size.

Table 1 shows the six categories in descending order according to adoption rate. The adoption rate refers to the percentage of the sources that stated using that coping strategy during a shortage. Of the eight sources strategies were obtained from, 100% of them adopted both making changes in imaging schedule and reducing ordered doses or eliminating “backup” doses as a necessary step in order to cope with a shortage. Implementing alternative imaging protocols was a strategy that a majority (75%) of the sources practiced during a Tc-99m/Mo-99 shortage and 37.5% of the sources mentioned generator management as being critical. A contractual agreement was disclosed by two sources as being the most important strategy for dealing with a shortage, which led to further investigation on the relationship between nuclear medicine departments and commercial nuclear pharmacies during a Mo-99/Tc-99m shortage. Finally, software utilization was found to be a Mayo Clinic specific approach. Although Mayo Clinic was the only source that acknowledged software utilization as being a key strategy, software utilization is a necessary in order to optimize the use of Tc-99m when the resource is scarce.

Although each outside source was asked to provide its “Top 3” coping strategies for a Mo-99/Tc-99m shortage, some sources provided more than three. This suggested that the strategies were all equally important, and therefore, these were included in the adoption rates.

DISCUSSION

Contractual Agreements with Commercial Nuclear Pharmacies

When selecting a nuclear pharmacy for radiopharmaceutical services, cost difference, customer service, preferable-customer status and proprietary products are amongst items to be considered. However, before signing a contract with a commercial nuclear pharmacy, it is important to look at the Mo-99 supply chain. In the United States, there are three generator manufacturers that are FDA approved: GE Healthcare (DryTec), Lantheus Medical Imaging (Technelite), and Mallinckrodt (Ultra-TechneKow DTE) (*6*).

When preparing for a shortage, both nuclear medicine departments and nuclear pharmacies should know how and where the Tc-99m was obtained. DryTec is used only in GE Healthcare commercial nuclear pharmacies. Other commercial nuclear pharmacies use either a Technelite (Lantheus) or Ultra-TechneKow DTE (Mallincrkodt) generator for Tc-99m. Both of these generator manufacturers obtain their Mo-99 from multiple sources. Lantheus receives Mo-99 from four major processors and six of the seven associated reactors, and Mallinckrodt receives their Mo-99 from five major world suppliers (*2,7*). This diversity allows stability in the Mo-99 supply if a source is interrupted. Although there is flexibility in the supply chain, shortages can still occur. Negotiating a contract that would allow the nuclear medicine department to be informed of their Mo-99 supply and alerted to any changes that arise, which would allow time to prepare for potential shortages. An optimal contract may also give an institution higher priority when Tc-99m is scarce. Therefore, while negotiating a contract, the logistics and timing has to be carefully evaluated.

Alternative Imaging Protocols

A common approach used during shortages is implementing different imaging protocols, such as reducing radioactivity administered or using alternate radiopharmaceuticals. The technological developments in gamma camera hardware allow for the potential for nuclear medicine exams to be performed using less administered radioactivity. This is beneficial to the patient, in regards to radiation exposure, while cutting costs and making more efficient use of the available Tc-99m. Reducing doses is a common approach, however, it does have some drawbacks. Image quality is reduced as a result of lower count rates; therefore, imaging time must be increased to accommodate for this. Increasing imaging time can then result in a chain of events, affecting camera availability, patient volumes and scheduling.

Employing alternate radiopharmaceuticals is often a better approach because it decreases the demand for Tc-99m while the same information is obtained from the images. One example would be using thallium-201 (^{201}Tl)-thallous chloride instead of ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin for myocardial perfusion imaging. Thallium is a potassium analog that is constantly pumped in and out of the myocardial cells via the sodium-potassium pump, making it an ideal agent for myocardial perfusion imaging. Due to its redistribution properties, ^{201}Tl may also be used for detecting viable tissue in the heart, which helps determine whether the myocardium can be re-perfused with surgery. However, ^{201}Tl is not a routinely used radiopharmaceutical due to some disadvantages: a longer half-life (73.1 hours) relative to Tc-99m resulting in higher radiation exposure to patients, poorer image quality due to the low energy mercury x-rays in the 68-80 keV range emitted during the decay of ^{201}Tl, and needing to have a camera available for immediate post-stress imaging before redistribution occurs to avoid false-negative findings. An advantage of ^{201}Tl-thallous chloride is that it is relatively inexpensive compared to Tc-99m, however, imaging with ^{201}Tl in some cases could result in an increased need for downstream testing, increasing both cost and patient radiation exposure (*8*). Another example would be using indium-111 (^{111}In)-labeled leukocytes instead of ^{99m}Tc-labeled leukocytes for infection imaging, including sites of inflammatory bowel disease and osteomyelitis. Although Tc-99m's photon energy, half-life, image quality, and lowered absorbed radiation dose to the patient are more ideal characteristics for a radiopharmaceutical, imaging with^{111}In-labeled leukocytes has its advantages. The biodistribution of ^{111}In-labeled leukocytes is different from that of ^{99m}Tc-labeled leukocytes. Unlike with ^{99m}Tc-labeled leukocytes, early imaging of the abdomen and pelvis is not critical since ^{111}In-labeled leukocytes do not normally accumulate in the bowel.^{111}In-labeled leukocytes are also advantageous in the case of osteomyelitis because simultaneous ^{111}In-labeled leukocyte/^{99m}Tc-medronate bone images may be obtained using multiple photopeak windows to differentiate the photons.

Changes in Imaging Schedules

Changes in imaging schedules include extending hours of operation, postponing, grouping and rescheduling patients, and eliminating exams. Extending hours of operation during periods of Tc-99m shortages beyond normal business hours and/or weekends makes more efficient use of the available Tc-99m. For example, patient schedules may be arranged to correspond to generator deliveries and elutions, allowing additional patients to be imaged on "hot" days when more Tc-99m is obtainable. Although available Tc-99m can be more efficiently used by extending hours, complications can arise with employee morale and facility hours of operation policies. These should both be considered if proposing hours of operation changes for a nuclear medicine department.

Postponing, grouping and rescheduling patients allows for both Tc-99m and kits to be saved by dedicating certain days of the week to certain exams. An example of this would be only performing bone scans on Mondays, Wednesdays and Fridays, and performing renal function imaging (^{99m}Tc-mertiatide or ^{99m}Tc-pentetate) on Tuesdays and Thursdays. Even though this decreases patient flexibility in scheduling, this would allow maximum utilization of the ^{99m}Tc-medronate (or ^{99m}Tc-oxidronate) kits by the nuclear pharmacy on Mondays, Wednesdays and Fridays, and eliminate the need for this kit to be compounded on other days of the week. When postponing, grouping and rescheduling patients, the emergent nature of the exams needs to be considered. Exams such as myocardial perfusion imaging should not be grouped, but rather should be available to be performed daily due to its use in demonstrating myocardial ischemia, and hibernating and stunned myocardium. Renal and bone imaging exams are often less emergent and, therefore, may be grouped, limiting the amount of kits needing to be compounded daily and thus reducing the need for Tc-99m.

Eliminating exams may also be a necessary step in order to reduce Tc-99m waste. An example of a study that results in a lot of Tc-99m waste is peri-ictal imaging of epilepsy patients. Nuclear medicine imaging has proven to be effective in locating seizure foci in the brain, using cerebral blood flow radiopharmaceuticals (^{99m}Tc-exametazime or ^{99m}Tc-bicisate) that have a rapid, first-pass extraction. This involves performing ictal and interictal SPECT imaging to identify a region of hyperperfusion in patients with focal epilepsy (*9*). For ictal imaging, a dose needs to be readily available for intravenous injection upon the sudden onset of a seizure, so an image can be produced showing the cerebral perfusion pattern that was present soon after the injection of the radiopharmaceutical (*9*). Although this is an important clinical application, peri-ictal imaging leads to unused doses, which results in Tc-99m waste.

As an alternative to nuclear medicine, other noninvasive, diagnostic-imaging modalities may be used, such as, computed tomography (CT) and magnetic resonance imaging (MRI). These diagnostic procedures are used to detect anatomical changes, while nuclear medicine procedures often identify physiological changes associated with disease. Often times, nuclear medicine can detect changes before any anatomical changes occur, allowing early identification of diseases and early evaluation of responses to therapeutic treatments (*10*). In the case of ictal/interictal imaging, CT, MRI and lumbar puncture may be used to localize the site of seizure onset (*11*). Although there are alternative modalities for localizing the epileptogenic focus, nuclear medicine proves to be the most superior modality, and therefore, these other modalities will not replace nuclear medicine ictal/interical imaging. In the case of cardiac imaging, there are six different procedures that can be used for diagnosing cardiac ischemia: myocardial perfusion imaging (MPI) SPECT, cardiac CT angiography, stress echocardiography, cardiac PET MPI, coronary artery calcium scoring and cardiac MRI perfusion (*10*). Tc-99m MPI SPECT accounts for 72% of cardiac imaging procedures in the United States, making it the most utilized cardiac imaging procedure (*10*). While determining which diagnostic modality to use for diagnosing cardiac ischemia, infrastructure (equipment and expertise), cost, and amount of reimbursement are more favorable factors for MPI SPECT (*10*).

There are some exams in which nuclear medicine provides unique clinical information and no alternatives exist. These studies should not be eliminated, but rather prioritized. This includes lung ventilation and perfusion imaging in patients with suspected pulmonary emboli, lymphoscintigraphy for sentinel lymph node localization, and identification of parathyroid adenomas. Although these studies require higher priority, changes may still be made, such as reducing administered dose, grouping and rescheduling patients. For example, coordinating with surgical staff to schedule lymphoscintigraphy patients the same day as surgery, rather than next-day surgery, can reduce the ^{99m}Tc in the dose.

Software Utilization

Specifically designed nuclear pharmacy software applications should be used to calculate theoretic activity and track Tc-99m usage by a department over time. Software programs that are commonly used to simplify ordering, streamline inventory receipts, and manage product documentation include ec^{2} Software Solutions applications, such as, BioRx designed for nuclear pharmacies and BioDose for nuclear medicine departments, Syntrac Integration Tools by Cardinal Health and Optility by Capintec Inc. (*12-14*). The initial cost, training required to learn a new system, and the additional time necessary to document Tc-99m usage are minimal compared to anticipated benefits of using these applications.

Although these software applications solely monitor Tc-99m usage and provide no information about what *should* be done with the available Tc-99m, they can be used to improve the selection of generator size and delivery schedules, if used applicably. Nuclear medicine technologists and nuclear pharmacists need to use the information gained from the software to make decisions about kit preparation and planning schedules. By using software applications to aid in decision-making, the utilization of daily and weekly Tc-99m radioactivity can be optimized for more efficient use of the available resource while reducing costs.

Generator Management

Generator management is important in Mo-99/Tc-99m shortages. Although it takes approximately 22.9 hours for Tc-99m to reach maximum activity after elution, elutions may be carried out before equilibrium is reached. Approximately 10% of the Tc-99m is produced per hour for the first ten hours after elution. Currently, many nuclear pharmacies either elute their generators once or twice a day. Increasing the frequency of generator elutions to several times throughout the day allows more activity to be obtained. As a result of more frequent elutions, more deliveries would be necessary.

While eluting a generator, fractionated elution is a technique that can be implemented to effectively obtain a high specific concentration of Tc-99m eluate. The volume of normal saline in the evacuated collecting vial can be altered based on the age of the generator to achieve a desired specific concentration. For example, when full elution yields are not needed, the volume of saline used for the elution can be decreased in order to increase the activity per volume concentration.

Reducing Ordered Doses or Eliminating “Backup” Doses

This is a common first approach for shortage situations. During these times, nuclear medicine departments often choose to triage doses as needed, thus reducing or eliminating standing orders prepared by the nuclear pharmacy. Another way to reduce unnecessary Tc-99m usage is eliminating “backup” doses. Often times “backup” doses are ordered to be available for add-on patients. Although these doses provide the opportunity for nuclear medicine departments to image “add-on” patients, often times they go unused and decay away. Therefore, in shortage situations nuclear medicine departments should eliminate ”add-on” orders to conserve Tc-99m.

CONCLUSION

The Mo-99/Tc-99m situation is continuously changing, so it is necessary to closely monitor it. A nuclear medicine department should establish standard operating procedures that can be promptly implemented if a shortage would occur. During a Mo-99/Tc-99m shortage, it is important to adequately manage the situation. Therefore, it is essential that a strong collaboration be formed between nuclear medicine departments and nuclear pharmacies. If both nuclear medicine departments and nuclear pharmacies preemptively implement these viable strategies, Tc-99m usage can be maximized during shortage situations.

DISCLOSURES

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TABLES

TABLE 1

Adoption Rates for the Six Categories of Viable Coping Strategies

Strategy	Adoption Rate (%)
Changes in Imaging Schedules	100
Reducing Ordered Doses or Eliminating “Backup” Doses	100
Alternative Imaging Protocols	75
Generator Management	37.5
Contractual Agreements with Commercial Nuclear Pharmacies	25
Software Utilization	12.5