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^{99}Mo shortage in nuclear medicine: crisis or challenge?

James R. Ballinger*

For the last 40 years ^{99m}Tc has been the workhorse of diagnostic nuclear medicine, because of its attractive physical characteristics (t1/2 6 h, γ energy 140 keV), convenience of on-site supply via a ^{99}Mo/^{99m}Tc generator, and the ability to image a variety of organ systems using chelates that can be prepared quickly, efficiently, reproducibly, and safely via 'kit' procedures. A generator is a closed, shielded, sterile, apyrogenic column of aluminium oxide loaded with ^{99}Mo (t1/2 66 h) and delivered to hospitals, generally on a weekly basis. Elution of the column with 0.9% sodium chloride yields ^{99m}Tc in a form suitable for the injection or preparation of a range of complexes. The worldwide demand for some 600 000 doses of ^{99m}Tc per week requires 450 TBq of ^{99}Mo, which is produced by fission of ^{235}U in only five nuclear reactors: NRU at Chalk River, Canada; HFR at Petten, the Netherlands; BR2 at Mol, Belgium; OSIRIS at Saclay, France; and SAFARI at Pelindaba, South Africa.[1,2] The OPAL reactor at Lucas Heights, Australia, has recently come on line and is gradually increasing its yield. Notably, there is no domestic production of ^{99}Mo in the USA or Japan, the two largest markets for nuclear medicine products.

Problems

The 5 reactors are all more than 40 years old and approaching the end of their useful lives. In each of the last 3 years there has been an emergency shutdown of one of the major reactors that has had a serious impact on the availability of ^{99}Mo worldwide. In November 2007 the NRU reactor was shut for regulatory issues; the resultant shortage rapidly crippled nuclear medicine in North America to an extent that the Canadian parliament passed legislation within a day allowing the reactor to resume operation without regulatory approval. In August 2008 the HFR reactor was shut due to corroded pipes and remained closed for 6 months; this was only a temporary fix and HFR will be closed for about 6 months in 2010 for additional repairs. In May 2009 the NRU reactor sprang a serious leak and had to be shut down and drained; after some initial uncertainty as to whether it could ever be repaired, it is scheduled to be back in operation in March 2010. The remaining reactors have struggled to ensure continuity of supply during this extended shutdown.

Public discomfort with radiation (the NIMBY syndrome) and international concern about nuclear proliferation have limited the construction of new reactors. Though most reactors have now converted to low enrichment ^{235}U (LEU, $<$20%) fuel they still use highly enriched ^{235}U (HEU) targets. HEU is considered weapons grade and its production, storage, and transport are highly regulated. Moreover, the USA will cease export of HEU within 7–10 years. There is no scientific reason that LEU targets cannot be used; indeed, the OPAL reactor uses LEU targets, as does the CNEA RA-3 reactor in Argentina. However, there are technical challenges in terms of greater volumes of material handled and waste generated.[1] The US government has recently passed the American Medical Isotopes Production Act which provides funding for a domestic supply of ^{99}Mo but stipulates rapid conversion to LEU targets.[3]

Logistical challenges

In the short term, radiopharmacies have struggled to make most efficient use of available ^{99}Mo. This can involve working extended days or weekends at times when ^{99}Mo is plentiful. Radiopharmacy is an extremely highly regulated area of practice, requiring compliance with a complex web of pharmaceutical and radiation regulations. Some sensible solutions fall afoul of both sets. For example, it might be logical for a large radiopharmacy to send a generator that no longer produces enough ^{99m}Tc for their requirements but is still within its expiry date to a smaller radiopharmacy where it might be perfectly adequate for another week. However, the pharmaceutical regulators will not let the smaller radiopharmacy accept the generator because its provenance is uncertain (i.e. not coming directly from a licensed manufacturer). Even shipping that generator can be problematic.

In some instances, other radionuclides can be substituted, for example ^{201}Tl thallous chloride for myocardial perfusion imaging. However, its imaging properties and dosimetry are far from ideal, which led to it being replaced by ^{99m}Tc agents 20 years ago, so this is clearly a retrograde step.

Requirements for ^{99}Mo can be further reduced by the use of image processing systems that recover spatial resolution from lower activity injections. This can be used with many current

Department of Nuclear Medicine, Guy's and St Thomas' NHS Foundation Trust; Faculty of Translational Medicine, NIHR Biomedical Research Centre, London; Division of Imaging Sciences, King's College London, UK

**Correspondence to: James R. Ballinger, Department of Nuclear Medicine, Guy's and St Thomas' Hospital, Great Maze Pond, London SE1 9RT, UK. E-mail: james.ballinger@gstt.nhs.uk*

generation γ cameras. In addition, newer cameras are being introduced which have more efficient solid-state detectors, allowing further reduction in administered activity.

Production challenges

Upgrading of current reactors, such as those at the University of Missouri and the Technical University of Munich could be achieved within 2–5 years at a cost of tens of millions of dollars, still far cheaper and faster than construction of new reactors. Replacement of the HFR and OSIRIS reactors is going ahead but will take 5–7 years.[4] Reactors in Argentina, Indonesia, Russia, Poland, and India could potentially take up some of the slack.

A variety of more speculative options are being considered. It has been suggested that a very old technology, ^{98}Mo(n, γ)^{99}Mo, could be made much more efficient by the use of enriched ^{98}Mo targets in order to increase specific activity (fission ^{99}Mo is carrier free).[2] Homogenous aqueous solution reactors have been around for years but may become economically viable for ^{99}Mo production in this new environment.[5] They offer the advantages of small size, less expensive construction and operation, and LEU fuel and targets, but their novelty as a source of radionuclides for medical use raises regulatory obstacles. Production of ^{99}Mo via particle accelerators has been proposed, most notably photo-fission of ^{238}U.[6] However, this requires extremely high intensity photons to overcome the low cross-section and accelerators with this power have not yet been constructed. Finally, the ^{100}Mo(p,2n)^{99m}Tc reaction can be performed in existing medical cyclotrons, or ones with slightly higher energy; this could be implemented within 2–3 years but would be only a local/regional solution.

Chemistry challenges

Much of the focus has been on devising alternative radiopharmaceuticals that would allow standard nuclear medicine γ or SPECT procedures to be performed using positron emission tomography (PET). The most practical cyclotron produced β^+ label is ^{18}F (t(1/2) 110 min) and novel methods are being developed for efficient incorporation of ^{18}F into a variety of biomolecules. Traditionally this has required a 2-step process (radiofluorination of active ester, coupling to protein/peptide), each of which may require purification, making the procedure lengthy and inefficient. Promising new approaches include click chemistry[7,8] and formation of aluminium fluoride which will efficiently label via chelation.[9]

However, it is the generator that frees radiopharmaceutical production from dependence upon a cyclotron and several generator systems for producing β^+ emitting radionuclides are available. Of these, ^{62}Zn/^{62}Cu (9 h, 10 min) is limited by the need for daily supply of ^{62}Zn, though a number of copper complexes have been explored.[10] ^{82}Sr/^{82}Rb (25 d, 75 s) is useful for myocardial perfusion imaging and cost effective with high throughput, but is not suitable for any other clinical applications. The greatest potential lies with ^{68}Ge/^{68}Ga (271 d, 68 min) where the generator has a useful shelf life of about 6 months, though further refinements in generator technology are required. Interest in ^{68}Ga complexes has increased greatly over the last few years.[11] Most clinical experience has been gained with somatostatin receptor binding peptides for imaging of neuroendocrine tumours, but these are relatively rare conditions.

The two highest volume clinical indications in nuclear medicine are myocardial perfusion imaging and bone scintigraphy. Although there are PET alternatives in use (^{82}Rb) or near the market (^{18}F-BMS-747158-02),[12] it should be possible to design a ^{68}Ga chelate with properties similar to the ^{99m}Tc complexes currently used for myocardial perfusion imaging.[13] Similarly, ^{18}F-fluoride can be used for bone scintigraphy but requires proximity to a cyclotron; the recent work of Torres *et al.* could be extended to the development of ^{68}Ga bisphosphonates.[14]

Concluding remarks

All of this has led to uncertainty about the future of ^{99m}Tc and traditional nuclear medicine. It has even been suggested that PET could completely replace γ imaging,[15] but I feel this is unrealistic for a variety of reasons. Although this may occur to some extent in the richer countries it is just not feasible for much of the world. It is difficult to put exact numbers on it, but PET radiopharmaceuticals have traditionally been at least 10 times more expensive than SPECT. Even if costs of ^{99}Mo production increase 5-fold, there is still a substantial margin. The expansion in availability of PET over the last 10 years has been based on a single radiopharmaceutical, ^{18}F-FDG. I don't think there is a full appreciation of the complexity (and cost) of supply of a range of short lived, cyclotron produced PET radiopharmaceuticals. Generator production would alleviate this somewhat, but supply is only one part of the equation. There is also the equipment: PET scanners are more expensive and less flexible than γ cameras. While PET will likely continue to expand, I feel that the current ^{99}Mo shortage crisis will force scientific and political solutions that will ensure the future of ^{99m}Tc. Both SPECT and PET chemistry will be enriched by meeting this challenge.

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