COMMENTARY

Short- and long-term responses to molybdenum-99 shortages in nuclear medicine

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ABSTRACT. Most nuclear medicine studies use $^{99}\text{Tc}^{\text{m}}$, which is the decay product of ^{99}Mo . The world supply of ^{99}Mo comes from only five nuclear research reactors and availability has been much reduced in recent times owing to problems at the largest reactors. In the short-term there are limited actions that can be taken owing to capacity issues on alternative imaging modalities. In the long-term, stability of ^{99}Mo supply will rely on a combination of replacing conventional reactors and developing new technologies.

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The demise of nuclear medicine has been predicted throughout the 30 years I have spent in the field. Yet, despite this, as Stephen Sondheim wrote, "I'm still here" [1]. The very name "nuclear" has negative connotations with the general public. Attempts to minimise this have led to the introduction in recent years of the term "molecular imaging", which encompasses most, but not all, nuclear medicine studies plus some MRI and optical techniques. However, this term is not universally embraced and it ignores the important contribution of nuclear medicine to radionuclide therapy.

Anti-nuclear feeling among the public has had another, more serious, impact on nuclear medicine. More than 80% of clinical nuclear medicine studies, planar or tomographic (e.g. single photon emission CT), use radiopharmaceuticals labelled with $^{99}\text{Tc}^{\text{m}}$ (half-life 6 h), which is produced by the decay of ^{99}Mo (half-life 66 h). Most of the world's supply of ^{99}Mo is obtained from only five ageing nuclear research reactors (Table 1), others having been decommissioned and not replaced because of the influence of the anti-nuclear movement [2].

All five reactors are reaching the end of their useful life. There are plans to replace the three European reactors, but it will be at least six years before the first of these is operational. Much hope had been placed in the construction of two Maple-X reactors at Chalk River (Canada), which were intended solely for medical isotope production. They would have operated in tandem with staggered downtimes providing a continuous supply (research reactors shut regularly for maintenance, refuelling and to modify the experiments). However, after years of delay and cost overrun, the Maple-X project was cancelled in 2008 and there are still questions

as to whether the new technology would ever have worked.

There appears to have been little co-operation between the services provided by reactor facilities in the scheduling of shutdowns for preventative maintenance. This situation has improved recently, but it can still be jeopardised when there is an emergency shutdown. In the last three years there has been a series of problems at the two reactors, that together produce 70% of the world supply under normal circumstances, culminating in an extended period during 2010 when neither was operating.

What is the problem?

^{99}Mo is produced by fission of highly enriched ^{235}U (HEU) targets in a nuclear reactor. In addition to the known radioactive waste problem, we face security issues with weapons-grade HEU. The USA will be phasing out the supply of HEU over the next few years [2]. Although there is no scientific obstacle to using low enrichment ^{235}U (LEU) targets, there are technical problems to be addressed, including the larger space required for the number of targets to be irradiated and the higher volume of waste produced by the process. However, these problems are not insurmountable, and production reactors in Argentina and Australia have already switched to LEU targets [2].

But irradiation of the target is only the first step in a supply chain that takes several days, during which time more than one-half of the ^{99}Mo decays. The five research reactors send their targets to only four sites that can extract and purify ^{99}Mo . The substance is then sent on to the relatively small number of generator production sites: two in the USA (half the world's market) and three in Western Europe. The generators are distributed to hospitals and

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Table 1. Major production reactors for supply of ^{99}Mo

Reactor	Location	Criticality date	Approximate % of world ^{99}Mo production
NRU	Chalk River, Canada	1957	40
HFR	Petten, the Netherlands	1961	30
BR2	Mol, Belgium	1961	10
OSIRIS	Saclay, France	1966	10
SAFARI	Pelindaba, South Africa	1965	10

central radiopharmacies, which obtain $^{99}\text{Tc}^{\text{m}}$ on a daily basis by “milking” the generator, and prepare the $^{99}\text{Tc}^{\text{m}}$ -labelled radiopharmaceuticals for injection.

Short-term responses

Alternative nuclear medicine studies

Over the years the most clinically useful nuclear medicine studies have flourished while others have been replaced by CT, MRI and advances in ultrasound. A specialised area of nuclear medicine – positron emission tomography (PET) – has expanded greatly in the last decade, largely thanks to the utility of 18-F-fluorodeoxyglucose in oncology. Hybrid PET/CT scanners are currently the highest-selling radiology equipment.

The two most widely used nuclear medicine studies (and the largest consumers of $^{99}\text{Tc}^{\text{m}}$) are bone scintigraphy and myocardial perfusion imaging. For bone scintigraphy there is a PET alternative using ^{18}F -fluoride, but current PET scanners do not offer sufficient capacity to take on this workload.

For myocardial perfusion imaging, many departments have reverted to ^{201}Tl – the radiopharmaceutical largely replaced by $^{99}\text{Tc}^{\text{m}}$ agents 15–20 years ago. ^{201}Tl is produced by cyclotron and so its availability is not affected by reactor shutdowns. The quality of ^{201}Tl images has improved owing to advances in gamma-camera design and performance, but there is a generation of nuclear medicine consultants who have never worked with ^{201}Tl . They will require training in the use of this radiopharmaceutical and its image interpretation. There is also a PET technique using ^{82}Rb , but it is expensive to implement and has the same PET capacity issues as bone scintigraphy.

While these are the largest volume studies, there are a number of other important areas where nuclear medicine provides unique clinical information and no practical alternatives exist. These include: lung ventilation/perfusion imaging of some groups of patients with a suspected pulmonary embolism; sentinel lymph node localisation; paediatric studies, especially renal; and localisation of parathyroid adenoma. Most of these require lower amounts of $^{99}\text{Tc}^{\text{m}}$ and can be prioritised in times of production shortage [3].

Alternative imaging modalities

Many nuclear medicine studies cannot easily be replaced by other imaging modalities. It is not just the issue of what is possible, but also which modalities have the capacity for the required throughput and concerns

around cost effectiveness and justifiable radiation dose. It is unlikely that CT or MRI departments in the UK have the capacity for 200 000 additional bone scans each year. Cardiac MR shows great promise for myocardial perfusion imaging, but it is unlikely that the service could handle 150 000 additional patients [4].

Coping strategies

While the ^{99}Mo shortage has been a worldwide problem, responses to it have varied from country to country. In the USA nuclear medicine staff have worked extended days and weekends when ^{99}Mo has been available. In the UK this seems to have happened only in areas where there is a fear of failing Department of Health targets. There are other steps that can be taken in radiopharmacies to maximise the use of available ^{99}Mo , but these require full-time staffing, which is not the usual practice in many departments.

Long-term responses

Changes in work patterns

Traditionally nuclear medicine has been a 9am–5pm weekday service, but this may no longer be defensible given that expensive equipment is being under-used and radionuclides are decaying away unused. However, the requirement for preparing radiopharmaceuticals in nuclear medicine makes delivering the service outside weekday working hours much more complex.

Changes in work patterns could apply to the industry as well. In Europe, generators are currently produced on a weekday schedule, meaning a significant portion of ^{99}Mo decay happens over the weekend. In contrast, the two suppliers in the USA produce generators on Sunday for first use on Monday morning, minimising the loss of ^{99}Mo through decay.

There are also some software techniques that can recover sufficient information density from gamma camera images after administration of smaller amounts of radioactivity (e.g. 50%), reducing the pressure on $^{99}\text{Tc}^{\text{m}}$ supplies. These techniques were originally developed to reduce imaging times with standard activities (i.e. increase throughput) and have not all been validated at standard imaging times with reduced activities.

Conventional technology

It is widely accepted that nuclear reactors are the most reliable source of ^{99}Mo and it is imperative that the three planned replacement reactors in Europe go ahead. The

USA, which consumes about one-half of the world's ^{99}Mo but has no domestic production, has started to rectify the situation, but it will take several years. This is likely to involve upgrading the University of Missouri research reactor in the first instance and new technologies are also being explored [2].

New technologies

The rise in cost of ^{99}Mo as a result of the shortage has reinvigorated new technologies that would not previously have been cost-effective. Some of these are highly speculative and, although feasibility studies have been funded, full-scale implementation may not be practical. Two particularly intriguing proposals involve neutron bombardment of ^{98}Mo targets in commercial nuclear power reactors [5] and direct production of $^{99}\text{Tc}^{\text{m}}$ in existing medical cyclotrons using the $^{100}\text{Mo}(\text{p},2\text{n})^{99}\text{Tc}^{\text{m}}$ reaction [6]. Each proposal faces very different technical challenges and, at this point it is difficult to predict which, if any, of these novel technologies will prove feasible.

Conclusions

For many years it has been said (mainly by the radiopharmaceutical industry) that $^{99}\text{Tc}^{\text{m}}$ is under-priced. That situation has certainly changed, with generator prices tripling in the last year and further increases expected if there is full economic costing of new reactors or alternative sources. We have also been through periods of shortage that none of us envisaged,

yet with hindsight were inevitable. Both the clinical importance and public profile of nuclear medicine have been strengthened by this crisis. We are not out of the woods yet, but the situation is beginning to stabilise.

In the short-term we must find ways to make our operations as flexible and responsive as possible, minimising barriers between imaging modalities and enabling regional co-operation among hospitals. In the long-term we must maintain pressure at all levels to ensure that the three European reactors are replaced and that potential alternative technologies are evaluated. We must do this to ensure the continuing availability of nuclear medicine services for our patients.

References

1. Sondheim S, Goldman J. *Follies: a musical*. New York, Random House: 1971.
2. National Academy of Sciences (USA). *Medical isotope production without highly enriched uranium*. Washington, USA, National Academies Press 2009.
3. Anonymous. *Current use and future needs of radiopharmaceuticals labelled with radionuclides produced in reactors and possible alternatives*. Document EMA/150127/2010. 2010, European Medicines Agency, London.
4. Wivell G, editor. *Cardiac imaging: a report of the National Imaging Board*. March 2010 UK. Department of Health, Gateway reference number 13859.
5. van der Marck SC, Koning AJ, Charlton KE. The options for the future production of the medical isotope ^{99}Mo . *Eur J Nucl Med* 2010;37:1817–20.
6. Guerin B, Tremblay S, Rodrigue S, Rousseau JA, Dumulon-Perreault V, Lecomte R, et al. Cyclotron production of $^{99}\text{Tc}^{\text{m}}$: an approach to the medical isotope crisis. *J Nucl Med* 2010;51:13N–16N.