Security of Supply of Medical Radioisotopes
- a clinical view

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Nuclear Medicine

- Approx 35 million clinical radionuclide imaging procedures worldwide

- Globally 2\textsuperscript{nd} most common imaging technique after CT (higher than MR)
  - 20 million in USA
  - 9 million in Europe
  - 3 million in Japan
  - 3 million in rest of the world

- Approx 700,000 nuclear medicine procedures per year in UK
Myocardial Perfusion - Ischaemia
Tc-99m Bone Scans

Normal

Metastases

Posterior

Posterior

Anterior
Mo-99/Tc-99m Generator Supply

- 99Mo decay – 66 h half-life
- 99mTc build up – 6 h half-life
- 99mTc elution
- Second elution

Timeline:
- 7am Tuesday
- 7am Wednesday
- 7am Thursday
- 7am Friday
- 7am Saturday
Mo-99 Shortages

WARNING!

RADIO INACTIVE

We select the letters for the envelopes from the rapid replies posted on line with the deadlines removed within five days of publication of the article to which they refer. Letters are then an early selection of rapid responses on a particular article. Readers should consult the website for the full list of responses and any authors' replies, which are usually available after our next deadline.

SHORTAGE OF MEDICAL ISOTOPES

Nuclear medicine services hit by shortage of molybdenum-99

Nuclear medicine departments throughout the world are facing the prospect of a severe shortage of molybdenum-99 over the next few weeks. Molybdenum-99 is delivered to hospitals weekly as the molybdenum/tellurium generator to produce the technetium-99m used in over 80% of routine diagnostic nuclear medicine investigations.

To suggest switches in bookings purely on the basis of waiting lists. Such actions may clash clinical priorities and result in suboptimal treatment for some patients.

Even when all the reactors are powered up there will be a delay before molybdenum production is fully reinstated. In the meantime, the nuclear medicine community will use the available limited resources in the fairest interests of clinical need (www.bmpms.org.uk).

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Competing interests: None declared.

FREE PRESCRIPTIONS IN WALES

Have dispensed items really risen with free prescriptions?

The headline in the print issue, "Free prescriptions in Wales lead to 5% rise in,

Radio inactive

The ageing of nuclear reactors is having a knock-on effect on hospital waiting lists. Supplies of an important medical isotope called molybdenum-99 are expected to dry up for the next months, delaying routine scans of hearts, bones and lymph nodes across Europe and the US.

Technical glitches and maintenance closures of reactors mean hospitals may receive just 50% of their usual supplies.

In the Netherlands has problems with its cooling system, and a nuclear plant in Canada closed temporarily last month due to a fire. Severe storms. The Canadian reactor also shut down in December, causing worldwide shortage of molybdenum-99. The shortage will last through September, and doctors are advised to delay nuclear imaging for non-urgent cases.

Making them talk

THE US military is training psychologists to interrogate terrorism suspects, in defiance of international treaty codes of conduct which bar doctors from involvement in interrogation.

British Medical Journal 2008;337:a1577
New Scientist 13 September 2008
Global supply of Molybdenum-99 (Mo-99) and Technetium-99m (Tc-99m) generators

1. U-235 targets
2. Reactors
   Target irradiation
3. Mo-99 facility
   Target dissolution and Mo-99 processing
4. Mo-99 bulk
5. Mo-99/Tc-99m generators

BR2
HFR
NRU
Osiris
Safari

Covidien The Netherlands
IRE
Nordion
NTP

Covidien USA

GE Health
IBA/CIS
Lantheus

Nuclear Medicine departments
Pharmacies
Design of Clinical Services to Reduce Tc-99m Use

- Optimisation of generator management
  - Efficiency savings
  - Delivery and extraction schedules
  - Patient scheduling

- Improved communication
  - Customers
  - Suppliers

- Improved software – gamma cameras
  - Produce comparable quality images using less radioactivity
OECD/Nuclear Energy Agency (NEA)

- Set up High Level Group (HLG-MR) in 2009
- Security of supply of Mo-99 and Tc-99m
- Established 6 principles e.g. full cost recovery and outage reserve capacity
- Issued a series of publications
Global Situation

- AIPES (Association of Imaging Producers & Equipment supplies)
  (Now called Nuclear Medicine Europe)
  - Support coordination of research reactor schedules
Global Situation

- Increased Mo-99 Production Capacity
  - Mo-99 suppliers – acquire additional capacity to cover shortfalls (Outage Reserve Capacity (ORC))
  - Supply capacity needs to equal market demand + ORC of 35% of market demand
    - e.g. Curium increased ORC at HFR, BR2 & Maria Reactors
      - Extra Mo-99 provided if unplanned maintenance in one of the reactors
      - Increased capacity at Mo-99 processing facility
**Global Situation**

- European Observatory on Supply of Medical Radioisotopes
  - Set up by AIPES in 2012
  - To monitor production and distribution of Mo-99/Tc-99m
Global Situation

- Enhanced communication between supply chain participants

- Development of back-up agreements between producers and irradiators
Currently ~9000 6-day Ci per week
  – Growth to 11,500 6-day Ci per week
  – Growth rates in mature markets ~ 0.5% through to 2021
Transition from HEU to LEU

- American Medical Radioisotope production Act 2012 encourages the use of non-HEU derived medical products (to enhance global security)

- Low-enriched uranium (LEU) is defined as U-235 < 20%

- Most HEU targets used in medical isotope production is > 90% U-235

- Medical radioisotope industry is converting the Mo-99 production process to the use of LEU

- Multiple cost components related to development and use of new LEU targets – upfront development, facility modifications, regulatory, operational, waste management/disposal
Status of LEU Conversion Efforts for Current Mo-99 Producers

Latest conversion update

**ANSTO**
- Began operation with LEU Targets

**NTP**
- Fully Converted to LEU Mo-99 now
- Fully Converted to LEU as of May, 2017

**Curiun**
- Fully Converted to LEU Mo-99 now
- Target and radiochemistry finalized
- Fully Converted to LEU as of Jan, 2018

**IRE**
- In process of converting to LEU Targets
- Target and radiochemistry finalized
- Expect to be Converted very late 2018 or 2019
Current main Mo-99 Reactors

SAFARI-1 Reactor
South Africa

Maria Research Reactor
Poland

LVR-15 REZ Reactor
Czech Republic

High Flux Reactor (HFR)
The Netherlands

OPAL Reactor
Australia

Nuclear Research Centre’s
Belgian Reactor 2 (BR2)
Belgium
Future Reactors for Mo-99 Production

- **FRM-II**
  - Germany
  - 2020

- **Jules Horowitz Reactor (JHR)**
  - France
  - 2022

- **KJRR (2023)**
  - Korea
  - (Domestic)

- **PALLAS (2026)**
  - replace HFR

- **RA10 (2021)**
  - Argentina
  - (domestic)
Global Mo-99 Processors

Curium
Located in the Netherlands

Institute for Radio Elements (IRE)
Located in Belgium

Nuclear Technology Products (NTP)
Located in South Africa

Australian Nuclear Science and Technology Organisation (ANSTO)
Located in Australia
New Alternative Technologies for Mo-99

Funded by US DOE/NNSA
~3000 6-day Curies Mo-99 each week

SHINE
Fission by shooting neutrons into uranyl sulfate solution

Niowave
Production of Mo-99 using superconducting electron accelerator

NorthStar Radiogenix Generator

Northwest Medical Isotopes
Fission using unique non-U metal targets
Direct Production of Tc-99m

$^{100}\text{Mo} \ (p, 2n) \ 99m\text{Tc}$
Canadian Research Site
Cyclotrons for Tc-99m Production

TR19
13-19 MeV,
Upgraded to:
300 μA

GE PETtrace
16MeV,
Upgraded to:
130 μA

TR24
Commercial Tc-99m production
500 μA
Enriched metallic $^{100}$Mo is acquired as a powder
- Natural abundance Mo is only 9.63% $^{100}$Mo
- Enrichment ~97 – 99+% $^{100}$Mo

Desired $^{100}$Mo specifications
- Purity and isotopic composition important
Dissolution and purification processes carried out in hot cells
- EC GMP Grade C

- $^{99m}$Tc pertechetate solution (~10-30 ml) terminally filtered (0.22 micron)
  - EC GMP Grade A

- Approximately 1 h for dissolution and purification
Quality Control of Products

- **Radiochemical purity**
  - >95\% for $^{99m}$Tc pertechnetate (complies with USP, Ph Eur and BP limits)
  - Radiolabelled kits complied with manufacturer’s limits for RCP

- **Assays**
  - Alumina - less than 5 ppm (complies)
  - Molybdenum (< 5 micrograms per ml)
  - Peroxide (< 1 microgram per ml)
  - pH – 4.5-7.5

- **Sterility, endotoxins and visual appearance**
  - comply with current pharmacopoeia limits
Radionuclidic Purity

- Dependent on target material, irradiation conditions and time after production at which the $^{99m}$Tc is used
  - Radionuclidic purity >99.9 %

- Influenced by the isotopic composition of $^{100}$Mo
  - More important than the absolute enrichment level
  - $^{94}$Mo, $^{95}$Mo, $^{96}$Mo and $^{97}$Mo are the significant contributors to the production of radionuclidic impurities
  - $^{100}$Mo can be sourced from Isoflex with 99.8% isotopic purity
    - $^{94}$-97Mo content below detection limit

- Small amounts of $^{93}$Tc, $^{94m}$Tc, $^{94}$Tc and $^{96}$Tc may be present
  - may contribute an additional radiation dose to the patient
Dinnington and Guildford to be expanded to accommodate ACSI TR24s as well as IBA18s

The TR24s will have dual targets to enable production of Tc-99m pertechnetate on the same day

Provide radiopharmaceutical supply to the NHS
Challenges

- Expiry time of cyclotron produced $^{99m}$Tc not yet determined
  - Envisaged it will be 12, 18 or 24 h from (End of Bombardment; EOB) production

- Logistics of supply of $^{99m}$Tc pertechnetate to Radiopharmacy Units
  - Time from cyclotron (EOB) to end of QC processes ~ 2h, then transport to Radiopharmacy Units for early morning production run
  - Shorter expiry time of pertechnetate e.g. 12 h from EOB may be problematic for radiopharmacies (kit expiry)

- Reliability of routine large scale cyclotron production of $^{99m}$Tc still needs to be demonstrated
  - Back-up arrangements

- Regulatory:
  - MHRA view is unknown
  - Licensing of cyclotron Tc-99m and existing kits?
BREXIT IS THREATENING OUR NHS

Euratom helps regulate and safeguard access to radioisotopes needed for cancer treatments

The NHS is having another winter crisis as thousands of EU staff leave

We need to stay in the EU and Euratom

www.HealthierIN.eu/Euratom
Legislative developments to prepare for EU exit

- The UK’s ability to import medical radioisotopes from Europe and the rest of the world will not be affected by our withdrawal from Euratom.

- As radioactive material, medical radioisotopes are captured by the Euratom Framework; however Euratom places no restrictions on the export of medical radioisotopes to countries outside the EU.

The UK already has robust, domestic regimes in place for the safety, security, transport, use and disposal of nuclear and radioactive materials – including medical radioisotopes – throughout their lifecycle. These regimes will remain in place when Euratom arrangements no longer apply in the UK, ensuring we exit with certainty, clarity and control.
Closure of Grove Centre 2019 (GE Healthcare)

- Major Mo-99/Tc-99m generator supplier
- Drytec generators
- Agreement with Curium to supply GE customers with generators
- GE to manage supply of Mo-99 and supply logistics for GE customers
- Loss of Cr-51 and Sr-89 products
DHSC

- Working closely with all suppliers of medical radioisotopes

- Avoid ‘short straights’ crossings (e.g. Dover to Calais)

- All short lived medicines (including radioisotopes)
  - use air freight
  - Changes to delivery schedules
Practical advice for radiopharmacy and nuclear medicine services in the event of a no-deal Brexit

In the event of an agreed UK withdrawal deal it is anticipated that supply will continue as it is now, without disruption.

However, should a no-deal Brexit become a reality, it is important services have a contingency plan to mitigate against any delays or disruption which may be experienced.

Radiopharmaceuticals are medicines, and the Government has been working with pharmaceutical companies to ensure that Brexit does not result in patients being unable to receive the medicines they need.

Much of the work done has been around stockpiling – and suppliers of radiopharmaceutical kits may well be doing this. However, clearly there are problems with doing this for the shorter lived radioisotopes used in many nuclear medicine studies.

Please note: this does not apply to PET-CT radiopharmaceuticals, which will continue to be delivered as usual. The vast majority of PET-CT radiotracers are not affected by Brexit as they are manufactured in cyclotrons throughout the UK or are produced outside the European Union, but there could be some issues with the delivery of PET-CT contrast agents.
Radiopharmacy/Nuclear Medicine Brexit Planning

- Review delivery schedules

- Keep patient workload light initially
  - Prioritise

- Therapy radioisotopes
  - Longer lived
    - Easier to accommodate

- Consideration of alternate imaging tests – initially

- PET Radioisotopes – not affected
Summary

- Significant improvements in production capacity of Mo-99

- Mo-99/Tc-99m supplies currently stable until at least 2022
  - Some fragility if unplanned reactor breakdowns

- Continuing development in new technologies
  - Long term sustainability

- No Deal Brexit planning
  - Still uncertainties
Thanks for listening

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