Cyclotron Production of $^{99m}$Tc

A. Zyuzin$^1$, B. Guérin$^1$, E. van Lier$^1$, S. Tremblay$^2$, S. Rodrigue$^2$, J.A. Rousseau$^2$, V. Dumulon-Perreault$^2$, R. Lecomte$^2$, J.E. van Lier$^2$

$^1$Advanced Cyclotron Systems Inc., Richmond, BC, Canada
$^2$Sherbrooke Molecular Imaging Center, Université de Sherbrooke, QC, Canada

Introduction. Current global interruptions of $^{99m}$Mo supply, aging reactors, and the staggering costs of their maintenance have accelerated the search for alternative sources of $^{99m}$Tc. Direct production of $^{99m}$Tc via $^{100}$Mo($p,2n$)$^{99m}$Tc nuclear reaction can be considered as one of such alternatives. The feasibility of $^{99m}$Tc production with a cyclotron was first demonstrated in 1971 by Beaver and Hupf and confirmed by a number of researchers. Measured yields indicate that up to 2.1 TBq (56 Ci) of $^{99m}$Tc can be produced in 12 h using a 500 μA 24 MeV cyclotron. This amount will be sufficient to cover population base of 5-7 million assuming: 15% $^{99m}$Tc losses, an average injected dose of 25 mCi and a 10 hrs decay. Initial results of the target development and thick target yields are presented in the “Mo-100 development for direct Tc-99m Production” abstract. In this work we compared the chemical and radiochemical properties and in vivo behavior of cyclotron- and generator-produced $^{99m}$Tc.

Experiment. Targets, 6-mm diameter discs, were prepared by melting $^{100}$Mo pellets (99.54% enrichment) onto tantalum backing supports. Targets were bombarded for 1.5–3 h with 14.5–17.0 MeV protons (14–52 μA), using a TR-19 cyclotron (ACSI). After bombardment, $^{100}$Mo targets were partially dissolved and purified by the method of Chattopadhyay et al. The radionuclide purity of the $^{99m}$Tc was >99.9%, as assessed by γ-spectroscopy, exceeding USP requirements for generator-based $^{99m}$Tc. Although small peaks corresponding to $^{99}$Mo were observed in the initial solute, these were not detectable in the purified $^{99m}$Tc-pertechnetate solution. Minute amounts of $^{97}$Nb were also quantitatively separated from during target processing. The content of other technetium isotopes was measured after allowing sufficient time (4 days) for $^{99m}$Tc decay. The presence of 0.0014% $^{98}$Tc and 0.0010% $^{95}$Tc at the end of bombardment, was below USP requirements of 0.01% for generator-produced $^{99m}$Tc. No other radionuclidic impurities were found. The radiochemical purity of cyclotron-produced $[^{99m}\text{Tc}]\text{TcO}_4^-$, as determined by instant thin-layer chromatography was >99.5%, well above the USP requirement of 95%. The content of ground state $^{99}$Tc ($T_{1/2} = 2.1 \times 10^5$ years) was not determined in these experiments and is one of the tasks for future work. For imaging studies, both cyclotron- and generator-produced $^{99m}$Tc were formulated as 3 different radiopharmaceuticals: $^{99m}$Tc-pertechnetate for thyroid imaging, $^{99m}$Tc-methylene diphosphonate ($^{99m}$Tc-MDP) for bone scanning, and $^{99m}$Tc-hexakis-2-methoxyisobutyl isonitrile ($^{99m}$Tc-MIBI) for heart imaging. These radiopharmaceuticals account for more than 75% of all routine $^{99m}$Tc scans currently used in diagnostic nuclear medicine. The latter two radiopharmaceuticals were prepared using commercially available kits. Labeling efficiency for the bone imaging agent $^{99m}$Tc-MDP and heart imaging agent $^{99m}$Tc-MIBI were 98.4% and 98.0%, respectively, well above USP requirements of >90%.

Animal Scans. The bio-distributions of $^{99m}$Tc-pertechnetate, $^{99m}$Tc-MDP, and $^{99m}$Tc-MIBI, prepared with either cyclotron- or generator-produced $^{99m}$Tc, were assessed in a healthy rat model. For each experiment 2 animals were simultaneously injected with a 0.3-mL physiologic saline solution containing 34–90 MBq of the selected $^{99m}$Tc-radiopharmaceutical, prepared either with cyclotron- or generator-produced $^{99m}$Tc. Dynamic acquisitions were continued over a 2 h period. At the end of scanning, the rats were killed and dissected to...
measure activities of target tissues. Static images obtained 2 h after administration of each of these 
$^{99m}$Tc-radiopharmaceuticals show matching $^{99m}$Tc distribution patterns, clearly delineating the 
thyroid with $^{99m}$Tc-pertechnetate, skeleton with $^{99m}$Tc-MDP, and heart with $^{99m}$Tc-MIBI (Fig. 1). Uptake kinetics calculated over the target organs (thyroid, bones, and heart), show identical uptake 
patterns for the cyclotron- and generator-produced $^{99m}$Tc-radiopharmaceuticals (Fig. 2). Tissue 
activities from dissected samples collected 30 min after the end of imaging with $^{99m}$Tc-MDP and $^{99m}$Tc-MIBI also show matching patterns between cyclotron- and generator-derived $^{99m}$Tc preparations (Fig. 3).

**Figure 2.** Time/radioactivity curves derived from regions of interest drawn around target organs (Fig.1) Dotted line: cyclotron-produced $^{99m}$Tc, Solid line: generator produced $^{99m}$Tc. Radioactivity is expressed as percentage of injected dose per unit area, corrected for radioactive decay.

**Figure 3.** Tissue uptake in healthy rats, expressed as percentage of injected dose per gram of tissue, 2.5 h after intravenous injection of 34 MBq of $^{99m}$Tc-MDP or 15 MBq of $^{99m}$Tc-MIBI, prepared from cyclotron-produced $^{99m}$Tc (open bars) or generator-produced $^{99m}$Tc (solid bars).

**Conclusion.** The results of these in vivo experiments and quality control tests support the concept that cyclotron-produced $^{99m}$Tc is suitable for preparation of USP-compliant $^{99m}$Tc radiopharmaceuticals. Establishing decentralized networks of medium energy cyclotrons capable of producing large quantities of $^{99m}$Tc may effectively complement the supply of $^{99m}$Tc traditionally provided by nuclear reactors, at a fraction of the cost of a single nuclear reactor production facility, while sustaining the expanding need for other medical isotopes, including short-lived positron emitters for PET imaging.

5. Lebeda, O. et al. New measurement of excitation functions for (p,x) reactions on $^{96}$Mo with special regard to the formation of $^{99m}$Tc, $^{96m+g}$Tc, $^{99m}$Tc and $^{99}$Mo. Appl. Radiat. Isot., in press