ORIGINAL ARTICLE

Assessment of molybdenum-99m content in 99Mo/Tc-99m generator: a clinical audit at Cancer Hospital

Muhammad Usman Ghani[1]*, Tooba Mujtaba[1], Kalim Ullah Khan[1], Saeed Ur Rehman[1], Mohammad Rauf[1], Abdur Rehman[1]

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ABSTRACT

Background: Nuclear medicine is a specialized field that employs radioisotopes for both diagnostic and therapeutic applications. Technetium-99m (Tc-99m), widely utilized in nuclear imaging, is eluted from a molybdenum generator. During this elution process, molybdenum (Mo) can occasionally contaminate the Tc-99m, compromising image quality and increasing patient radiation dose. The measurement of molybdenum contamination, referred to as the molybdenum breakthrough test (MBT), is critical to ensure safety and compliance with international standards.

Aim and Objective: This study aimed to evaluate and report the MBT data collected over 10 years at the Atomic Energy Cancer Hospital, Bannu, to assess adherence to international limits and trends in molybdenum breakthrough.

Methods: MBT data were collected from 5th November 2013 to 30th December 2023 using a dose calibrator (CRC-25R) and standard molybdenum canisters for each elution from molybdenum generators. Data were analyzed using standard statistical methods to determine compliance with the internationally recommended limit of 0.15 µCi of 99Mo/mCi of 99mTc.

Results: The analysis revealed that molybdenum contamination levels consistently remained below the recommended threshold. The mean MBT value was 0.018 ± 0.023 µCi of 99Mo/mCi of 99mTc, with a standard error of the mean of 0.006%.

Conclusion: The findings indicate that the molybdenum breakthrough levels at the institute complied with international safety standards over the studied decade, demonstrating a high standard of quality control in generator elution procedures.

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Address for correspondence: Muhammad Usman Ghani
*Senior Scientist, Atomic Energy Cancer Hospital, Bannu Institute of Nuclear Medicine Oncology and Radiotherapy (BINOR), Bannu, Pakistan.
Email: mug1771@gmail.com
Full list of author information is available at the end of the article.

Introduction

The short-lived ^{99m}Tc ($T^{1}/_{2}$ = 6 h), eluted from the ^{99}Mo/^{99m}Tc generator as a daughter product of long-lived ^{99}Mo (half-life = 67 h), has played a pivotal role in the growth of diagnostic nuclear medicine [1]. The Technetium-99m generator was initially developed by Walter Tucker and Margaret Greene at the Brookhaven Hot Laboratory Division in 1958, with Richard first proposing its use as a medical tracer [2]. Various ^{99m}Tc complexes are widely used in diagnostic procedures, with approximately thirty agents employed in clinical studies [3]. Currently, over 80% of radiopharmaceuticals are labeled with this radionuclide. The ^{99}Mo isotope decays by isomeric transition to ^{99m}Tc, which is why the generators are often referred to as ^{99}Mo/^{99m}Tc generators [4].

Molybdenum contamination in the ^{99m}Tc eluate, known as molybdenum breakthrough, is a critical parameter that can significantly impact patient safety. Due to the long half-life (66 hrs) and high-energy beta rays (1.214 MeV) and gamma rays (740 keV and 780 keV) associated with ^{99}Mo, contamination can increase the radiation dose to patients while degrading image quality [5]. The radionuclide purity of ^{99m}Tc eluates is evaluated by assessing the molybdenum breakthrough, which is defined as the ratio between ^{99}Mo and ^{99m}Tc in the eluate [6]. Regulatory guidelines stipulate strict limits for molybdenum contamination. The European Pharmacopeia recommends that the activity concentration of molybdenum should not exceed 1 kilobecquerel per 1 megabecquerel of Technetium-^{99m} [7]. Similarly, the U.S. Pharmacopeia (USP) and the U.S. Nuclear Regulatory Commission (NRC) enforce a threshold of 0.15 µCi of ^{99}Mo per 1 mCi of ^{99m}Tc [8]. The limit recommended by the International Atomic Energy

Agency (IAEA) is the same as the USP guideline. High levels of ^{99}Mo in the eluate can be reduced by passing the contaminated Technetium through an old generator [9].

Quality control of radiopharmaceuticals is essential to ensure safety, efficacy, and compliance with these international standards. Techniques such as the molybdenum breakthrough test (MBT) are used to evaluate the radionuclide purity of ^{99m}Tc eluates. High-purity Germanium detectors and ionization chambers (dose calibrators) are commonly employed to measure ^{99}Mo contamination [10]. Clinical audits of molybdenum breakthroughs provide valuable insights into the effectiveness of quality control systems and help improve healthcare outcomes. In previous studies, radionuclide impurities in ^{99m}Tc eluates have been assessed for both indigenous and imported generators, revealing that only a small percentage exceed the recommended molybdenum levels [11-13].

The primary aim of this study was to assess the molybdenum contamination in ^{99m}Tc generators manufactured by the Isotope Production Division of PINSTECH, Islamabad, Pakistan, over ten years (2013-2023). The study seeks to evaluate the compliance of molybdenum levels with international pharmacopeial standards, highlight the reliability of quality control systems, and provide recommendations for improving radiopharmaceutical generators' manufacturing and distribution processes.

Materials and Methods

The elution of all the 100 ^{99}Mo /^{99m}Tc Generators received at BINOR was performed from 2013-2023 on consecutive six days a week. The CRC-25R (CAPINTEC, Inc. USA.) dose calibrator was used to measure the activity. It is recommended that the MBT test be performed to assess the amount of ^{99}Mo content with the standard lead canister and insertion holder. The thickness of the lead canister is 1.3 cm(or 0.5 Inches as per Capintec CRC-25R manual) to stop the 144 keV photons radiation from the eluted technetium and only the 346 keV photons of molybdenum are detected in the well chamber. The well chamber is calibrated using a Cs-137 source. The international limitation of the ^{99}Mo content is 0.15u Ci of moly per mCi of ^{99m}Tc as follows:

$$\frac{Moly}{content} = \frac{Moly\ Activity\ in\ Elute\ (\mu Ci)}{Tc-99m\ Activity\ in\ the\ elute\ (mCi)} \leq 0.15.$$

The moly-generator of activity 300 mCi started to elute on the first day of the week. The MBT is performed for each elution. If moly content is found higher than the recommended limit, the eluate is passed through an old generator so that the moly adsorbs at the alumina column and MBT is again performed. The data were collected for ten years (2013-2023) and results were plotted. The statistical evaluation was done using Statistical Package for the Social Sciences (SPSS) Version 16.

Results

In the MBT, a comprehensive analysis was conducted on a sample size of 1397 of 11 years from 2013 to 2023. The average breakthrough was determined to be 0.018, with a measure of variability represented by a standard deviation of 0.023 and a standard error of the mean of 0.000624 as shown in Table 1. The valid percentage frequency with particular ^{99}Mo content is also shown in Figure 1.

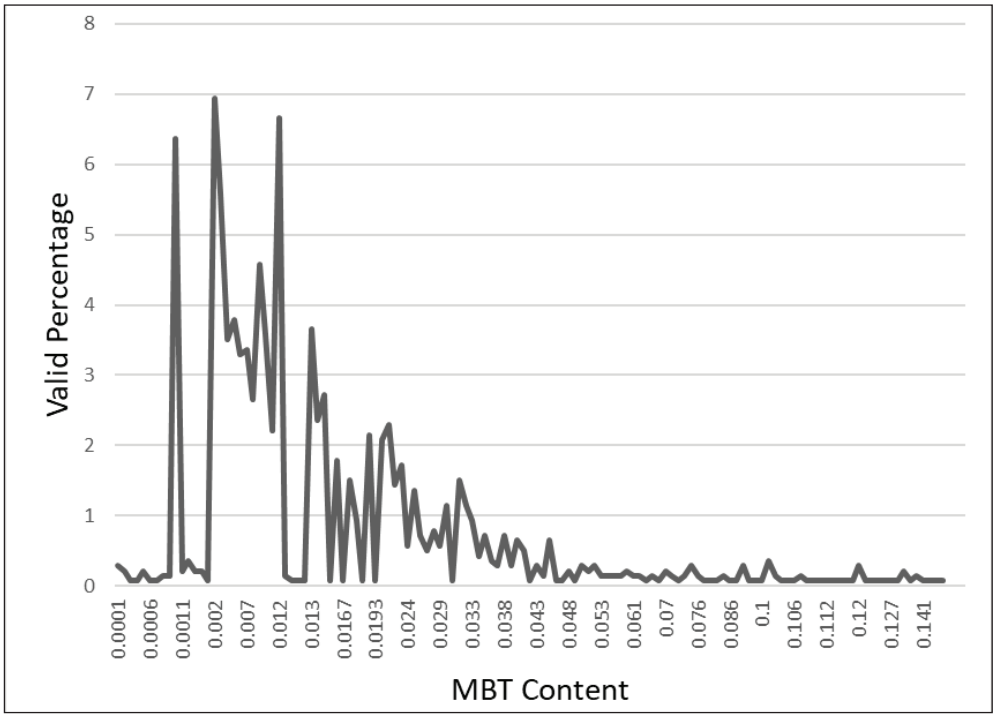

***Figure 1**. Valid percentage % of a particular MBT content (µCi of Moly/mCi of ^{99m}Tc).*

To evaluate the significance a one-sample t-test was conducted. The results in Table 2. show a *t*-value of 29.383 with 1396 degrees of freedom, which was very significant ($p < 0.001$). The average difference was 0.018, with a 95% confidence interval spanning from 0.017 to 0.020, suggesting a significant deviation from the null hypothesis.

In addition, a chi-square test was used to evaluate the distribution of breakthrough values as shown in Table 3. The chi-square value was 4.457E3 with 128 degrees of freedom ($p < 0.001$), indicating a substantial deviation from the predicted distribution. The molybdenum level in the elution at BINOR is within acceptable limits, and the data shows a consistent trend toward decreasing amounts of ^{99}Mo in the elution. The results emphasize the efficacy of the MBT in maintaining molybdenum concentration within acceptable limits, showcasing BINOR's dedication to quality control in the manufacturing of radiopharmaceuticals.

Discussion

The results of the MBT carried out at BINOR Cancer Hospital provide significant knowledge on the reliability and safety of molybdenum levels in elution. The average breakthrough value of 0.018337, backed by a significant sample size of 1397, indicates that PAKGEN produced by PINSTECH is safe to use for human administration. The one-sample t-test demonstrates the strong statistical significance of the MBT in identifying breakthrough events, with a t-value of 29.383 ($p < 0.001$). The test demonstrates a mean difference of 0.018, which is supported by a tight 95% confidence range ranging from 0.017 to 0.020. This emphasizes the high level of accuracy in the test and the confidence in its results. The chi-square test, which assesses the distribution of breakthrough values, indicates a substantial deviation from the anticipated distribution (chi-square value of 4.457E3, $p < 0.001$). This suggests that the observed breakthrough occurrences are not happening by chance, which strengthens the consistency in keeping molybdenum levels below the specified threshold. The constant decrease in molybdenum levels throughout elution is a positive finding. It adheres to globally authorized limits and underscores BINOR's dedication to rigorous quality control methods. The findings confirm that the molybdenum level in the hospital is consistently within the stipulated limit of 2%, guaranteeing the safety and effectiveness of radiopharmaceuticals given to patients.

To summarize, this research provides a thorough analysis that shows how the MBT effectively ensures the quality and safety of molybdenum levels at BINOR Cancer Hospital. These results aid in the continuous endeavors to augment radiation therapies' accuracy and dependability, enhancing patient outcomes. Subsequent investigations might delve into more precise testing procedures or include supplementary variables to continuously progress the radiopharmaceutical quality assurance domain.

Table1. *Frequency Table of MBT data.*

One-Sample Statistics				
	N	Mean	Std. Deviation	Std. Error Mean
MBT	1397	0.018	0.023	0.00062

Table 2. *T- Test Statistics of MBT data.*

One-Sample Test						
	Test value = 0					
	t	df	Sig. (2-tailed)	Mean difference	95% Confidence interval of the difference	
					Lower	Upper
MBT	29.383	1396	< 0.001	0.0183374	0.017113	0.019562

Table 3. *Chai-square test of MBT data.*

Test Statistics	
	MBT
Chi-square	4.457E3[a]
Df	128
Asymp. Sig.	< 0.001
a. 0 cells (.0%) have expected frequencies less than 5. The minimum expected cell frequency is 10.8.	

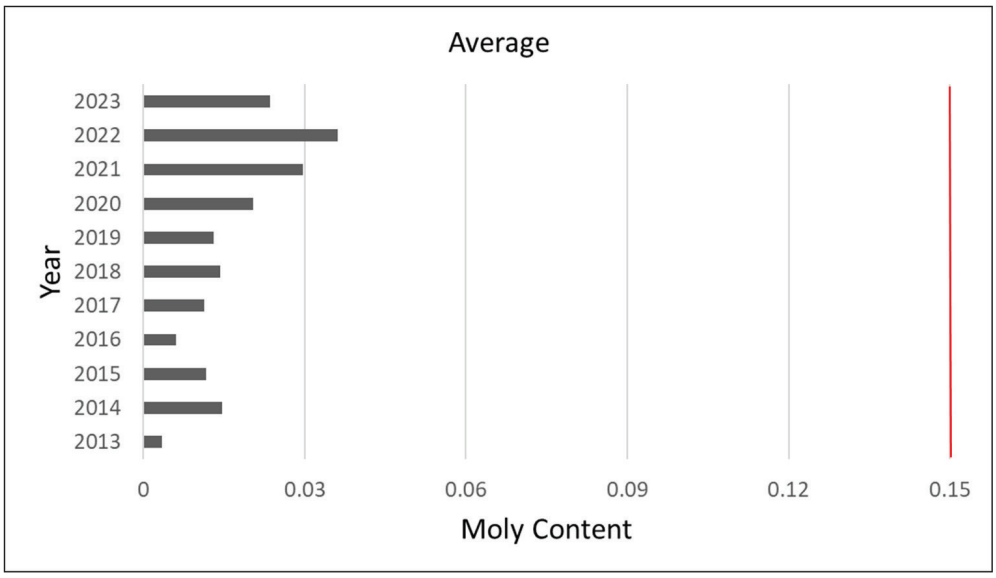

Figure 2. *Annual average MBT content comparison.*

Conclusion

This research paper offers a thorough evaluation of molybdenum impurity in ^{99m}Tc generators manufactured by PINSTECH from 2013 to 2023. The research highlights the importance of the MBT as a critical element in guaranteeing the safety and effectiveness of radiopharmaceutical administration to humans.

The results confirm the dependability of PAKGEN generators since they constantly meet the strict limitations for molybdenum concentration set by international pharmacopeia regulations. The comparatively low occurrence (1.8%) of MBT tests indicating increased molybdenum levels confirms the overall strength and proper upkeep of the generators.

Nevertheless, the research emphasizes the need to be vigilant throughout the manufacturing and transportation operations due to the possibility of encountering faulty alumina columns. This study makes a major contribution to the area of nuclear medicine by highlighting the utmost need to follow quality assurance criteria for ^{99m}Tc generators. The knowledge acquired from this research will assist in improving processes and guaranteeing the ongoing safety and effectiveness of radiopharmaceuticals in clinical use.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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None.

Consent for participate

Not applicable.

Ethical approval

Ethical approval was granted by Ethics Committee Pakistan Atomic Energy Commission, Bannu Institute of Nuclear Medicine Oncology & Radiotherapy (BINOR) via reference BINOR-E4 (40)/12, dated: 4-03-23.

Author details

Muhammad Usman Ghani[1], Tooba Mujtaba[1], Kalim Ullah Khan[1], Saeed Ur Rehman[1], Mohammad Rauf[1], Abdur Rehman[1]

1. Atomic Energy Cancer Hospital, Bannu Institute of Nuclear Medicine Oncology and Radiotherapy (BINOR), Bannu, Pakistan

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