Original Article

Radiation Dose to the Occupational Worker during the Synthesis of ^{188}Re-labeled Radiopharmaceuticals in the Nuclear Medicine Department

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Abstract

Aim: The aim of this study is to estimate whole-body radiation dose to the radiopharmacist involved in labeling of three different ^{188}Re-labeled compounds, namely, ^{188}Re-Lipiodol, ^{188}Re-tin colloid, and ^{188}Re-hydroxyl-ethylidene-diphosphonate (HEDP) and to compare the occupational burden with the dose limits recommended by Atomic Energy Regulatory Board, India. **Materials and Methods:** The Department of Nuclear Medicine at Fortis Memorial Research Institute currently synthesizes three different Rhenium-188 labeled compounds, namely, ^{188}Re-Lipiodol, ^{188}Re-HEDP, and ^{188}Re-tin colloid. To estimate the radiation exposure to the radiopharmacist involved in the synthesis, a survey meter was used to measure radiation level before the start of labeling procedure in the radiopharmacy by keeping it at the location where the radiopharmacist normally stands during preparation. Data were collected for 6 syntheses of each ^{188}Re-Lipiodol, 4 for ^{188}Re-HEDP, and 3 for ^{188}Re-tin colloid followed by the quality control. The pocket dosimeter was used by the radiopharmacistat chest level, performing the labeling of ^{188}Re-labeled compounds. All radiopharmaceuticals were synthesized by a single radiopharmacist. **Results:** 1850 MBq (50 mCi) ^{188}W-^{188}Re generator was eluted before the preparation of each radiopharmaceutical. The amount of ^{188}ReO4^{-} used for labeling with lipiodol/4-hexadecyl-1,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol, HEDP, and Tin colloid was in the range of 3182–4440 MBq (86–120 mCi), 2812–3774 MBq (76–102 mCi), and 962–1295 MBq (26–35 mCi), respectively. Meantime required to complete the synthesis was 95, 40, and 131.5 min, respectively. Mean whole-body effective dose received was 0.052, 0.009, and 0.004 mSv, respectively, as measured by using the pocket dosimeter. **Conclusion:** From this small study, we observed that the whole-body radiation dose to the radiopharmacist in radiolabeling and quality control of ^{188}Re-labeled radiopharmaceuticals is within prescribed limits at the current synthesis frequency.

Keywords: *Radiation dose, radiopharmacy, Re-188*

Introduction

Rhenium-188 (^{188}Re) is a generator produced beta-emitting radioisotope which has shown utility for a variety of therapeutic applications in nuclear medicine. ^{188}Re is obtained from ^{188}W/^{188}Re generator and decays with a half-life of 17 h which is long enough for the therapeutic purpose and short enough to give extra radiation high energy β^{-}burden. It emits both a gamma photon ($E\gamma$ = 155 keV) which is easily collimated by a low-energy collimator and a beta particle with the maximum energy $E\beta$maximum of 2.11 MeV (average range in soft tissue-3 mm) which is well suited for treating solid tumors. These favorable physical and radiation characteristics, easy logistics, and availability in a pyrogen and carrier free state have made it suitable option for clinical use.[1] At our center, at the Fortis Memorial Research Institute (FMRI), Gurgaon, we are routinely synthesizing Re-188 labeled radiopharmaceuticals such as ^{188}Re-hydroxyl- ethylidene -diphosphonate(HEDP), ^{188}Re-4- hexadecyl -1,2,9,9-tetramethyl-4, 7-diaza-1, 10-decanethiol (HDD)/lipiodol and ^{188}Re-tin colloid for bone pain palliation, hepatocellular carcinoma treatment and radio synovectomy, respectively.

Estimation of exposure to the occupational staff involved in the synthesis of radiopharmaceuticals, dose administration, and scan acquisition was thought to be essential as a part of radiation safety practice. In view of the potential hazard associated with the ionizing radiation, these practices are subject to regulatory control. Several national and international regulatory authorities have laid down safe

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radiation work practices and permissible radiation exposure limits. The government of India provides the statutory basis in the form of Atomic Energy Act 1962, and the rules are promulgated by the Atomic Energy Regulatory Board (AERB). According to ICRP recommendations 103 (2007), any person handling radiation and likely to receive an occupational radiation exposure of more than 1 mSv is liable to be monitored and the equivalent radiation dose to personnel should not exceed 20 mSv/year averaged over 5 years, not exceeding 50 mSv in any year,[2] but the upper limit is 30 mSv according to AERB in India.

With the multifarious application of ^{188}Re-labeled products, monitoring radiation exposure to the radiopharmacist involved become a prime concern. The objectives of the present study hence were to assess the whole-body radiation doses received by radio pharmacists while synthesizing ^{188}Re-labeled products and to compare the occupational burden with the dose limits recommended by AERB, India.

Materials and Methods

W-188/Re-188 generator

A 1850MBq ^{188}W-^{188}Re generator was procured from ITG, Germany. The generator was eluted as and when required to obtain Na^{188}ReO4^{-} in a pyrogen and carrier free form.

Dosimeter and readout system

A digital pocket dosimeter (MyDose Mini – G 9679) was obtained from ALOKA to measure the dose received. The dosimeter was calibrated by Nuvia India in January 2017. The applied radionuclide for calibration was Co-60. The applied dose was 19.834, and the background subtracted observed reading was 18.498 which showed a relative intrinsic error of − 6.74%. A survey meter (Inspector – SN# 28592) was used for the general survey. It was also calibrated by Nuvia India in January 2017. It was also calibrated by Co-60 and showed a relative intrinsic error of 10%–13% at different applied exposure rate.

Chemicals

The precursors used in the synthesis of ^{188}Re-labeled HDD/Lipiodol were obtained from ABX GmbH, Germany, and HEDP kit was obtained from Polatom. All other reagents used in labeling were of analytical grade.

Exposed personnel

Synthesis of Re-188 labeled HDD/Lipiodol, HEDP and tin colloid was carried out by designated skilled personnel at the radiopharmacy laboratory of the Department of Nuclear Medicine, FMRI, Gurgaon, Haryana, India. Radiopharmacist stood behind the L-bench during preparation with a lead equivalent glass insert and took care of the three cardinal principles of radiation safety and followed the time, distance, and shielding approach to minimize the radiation exposure. Data were collected for 6 syntheses of ^{188}Re-HDD/Lipiodol, 4 for ^{188}Re-HEDP, and 3 for ^{188}Re-tin colloid followed by the quality control procedure.

Procedure

A survey meter (Inspector) was used to measure the radiation level in the radiopharmacy laboratory before the start of labeling procedure by keeping it at the location where the radiopharmacist normally stands during preparation. The radiation survey meter was calibrated at the accredited laboratory Nuvia (India). The survey meter was also checked periodically for its accuracy by measuring the exposure rate at 2 meters from the known activity of I-131. The pocket dosimeter (MyDose mini-ALOKA) was given to the radiopharmacist performing the labeling of Re-188 labeled compounds which was placed at chest level. All radiopharmaceuticals were synthesized by a single radiopharmacist to avoid any operator discrepancy. Radiopharmacist performed three steps of task in the preparation Re-188 pharmaceuticals. The first step was the elution of activity from the generator. It was done with three different volumes of saline - 2 ml, 1.5 ml, and then 2.5 ml. The first sample of 2 ml was usually discarded and then, the remaining activity was used according to the requirement. The total amount of radioactivity handled during labeling and the duration of each labeling procedure was noted. The second step was to perform the labeling according to the protocols which involves mixing, heating, and finally, the dose dispensing. The third step was to perform the quality control procedures. Radiochemical purity was determined by thin layer chromatography using different solid and mobile phases. The total radiation dose received by the radiopharmacist was timed from the first step and ending when the radiopharmacist finally prepared the dose for injection. The amount of activity eluted and the dose received during elution was also noted separately as the amount of activity eluted and used for synthesis was sometimes different. The radiation doses received by the radiopharmacist were read directly from the dosimeter and time and dose for each step was recorded.

Labeling procedures

For ^{188}Re-HEDP, 2960–3700 MBq (80–100 mCi) ReO4^{-} in 1–2 ml was added to the cold kit and the reconstituted solution was then heated in boiling water for 25 min. After heating, the solution was allowed to cool at room temperature and following that 2 ml of acetate buffer were added. Radiochemical purity was determined using Whatman paper no. 1 as solid phase and saline and acetone as mobile phases. The percentages of different entities were determined and a labeling efficiency of >95% was ensured before intravenous injection into the patient.

For ^{188}Re-HDD/Lipiodol, 3700–4440 MBq (100–120 mCi) ReO4^{-} in 1–2 ml was added to the HDD kit and vortexed for 5 min. The mixture was heated in water bath at 100ºC for 60 min. Following heating, 3 ml Lipiodol was added

to the vial and vortexed again for 10 min. The resulting solution was then centrifuged at 300 rpm for 10 min to separate the aqueous and organic layer. Finally, the aqueous layer was removed, and ^{188}Re-Lipiodol was harvested. If required, more Lipiodol was added and the whole procedure of mixing, centrifugation, and separation were followed. For quality control, the same protocol was followed as that of ^{188}Re-HEDP.

For ^{188}Re-Tin colloid, 0.5 ml of required amount of ^{188}ReO4^{-} (370–740MBq, 10–20 mCi) was added into a clean vial containing 0.5 ml of freshly prepared stannous chloride solution. The solution was mixed well and heated at 100ºC for 2 h. After cooling, required amount of 0.2 M phosphate buffer was added to adjust the pH of the final solution to 8. For quality control, the thin-layer chromatography silica gel (ITLC) strip with the sample was developed in saline and activity associated with each segment was determined.

Statistical analysis

Descriptive statistical analysis was performed for the collected data; and mean, median, standard deviation (SD), and range (minimum to the maximum value) were determined. All the readings were expressed as mean ± SD.

Results

The readings of the survey meter were 0.03 ± 0.01 mSv/h in the radiopharmacy laboratory. The survey meter was found to be accurate as the exposure rate at 2 m from 1 mCi of I-131 was 0.62 mR/h (i.e., within 20% of the expected value [0.55 mR/h]). The generator was eluted thirteen times during its shelf life and the radiation dose received during elution was assessed in the study [Figure 1]. The amount of ^{188}ReO4^{-} used for labeling with HDD/Lipiodol, HEDP, and Tin colloid was in the range of 3182–4440 MBq, 2812–3774 MBq, and 962–1295 MBq, respectively. The radiation dose received during eluting the generator was in the range of 7–16 μSv [Table 1]. The mean activity eluted from the generator was 4314 MBq (116 mCi) and the mean dose received during the elution was 11.5 μSv [Table 1]. The mean radiation dose recorded in synthesis of ^{188}Re-Lipiodol was 0.052 ± 0.004 mSv [Table 2], ^{188}Re-HEDP was 0.009 ± 0.004 mSv [Table 3], and ^{188}Re-Tin colloid was 0.004 ± 0.001 mSv [Table 4]. Mean duration of labeling was 95 min, 40.5 min, and 131.5 min, respectively. The time required for quality control using ITLC for all the synthesis was same, i.e., 10 min and the mean radiation dose received during quality control was 3 μSv. However, the total dose received for all 13 procedures using 56 GBq (1516 mCi) ^{188}ReO4^{-} was 786 μSv acquired over a period of 6 months. The highest exposure was incurred in the synthesis of ^{188}Re-Lipiodol and the doses were highest during eluting the generator followed by the dose dispensing [Figure 2].

Discussion

The utility of Re-188 for treating various diseases has greatly increased by the development of an in-house ^{188}W/^{188}Re-generator by which Re-188 can be obtained in a carrier free state as Na^{188}ReO4^{-}. Parent radionuclide, tungsten-188 (W-188) has a half-life equal to 69.4 d and Re-188 has attractive physical and chemical properties by which it can be labeled to a variety of compounds for the diagnostic as well as therapeutic use. A1850 MBq (50 mCi) generator was procured in the department in FMRI and this study was conducted to determine the whole-body doses received by the personnel involved in the labeling of ^{188}Re-radiopharmacy, since there is paucity of literature regarding occupational exposure during synthesis of Re-188 radiopharmaceuticals. Three radiopharmaceuticals: ^{188}Re-HEDP, ^{188}Re-Lipiodol, and ^{188}Re-Tin colloid were synthesized over the shelf life of the generator. Andreeff *et al*. [3] in a study measured the dose received by the radiochemist involved in the labeling of ^{188}Re-Labeled pharmaceuticals using ring dosimeters. They revealed that the true radiation dose to the skin of the fingertips exceeds by far the readings of the official ring dosimeters as well as the continuously readable beta- and gamma-dosimeters. They also suggested risk in exceeding the radiation limit of 500 mSv/a given in the German Radiation Protection Law (section sign 5).

The study results showed that the labeling of ^{188}Re-Lipiodol yielded the highest mean radiation dose of 0.052 ± 0.01

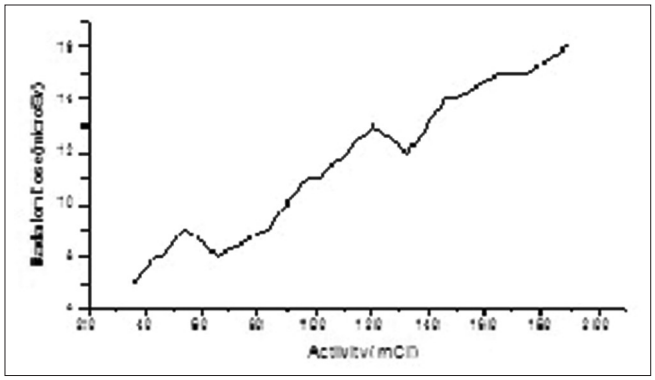

Figure 1: Amount of activity eluted and the radiation dose received by the radiopharmacist during elution of the generator

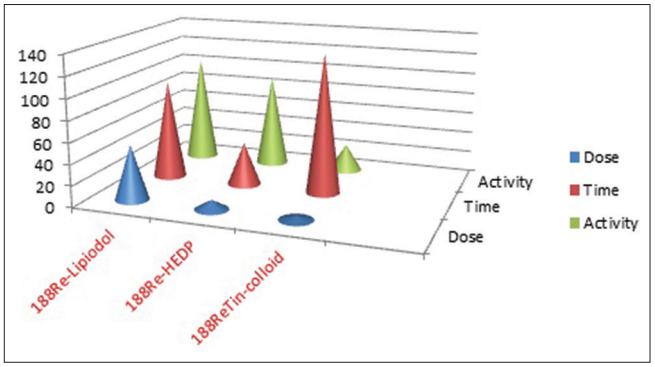

Figure 2: Comparison of activity handled, time utilized and the dose received by the radiopharmacist for different ^{188}Re-radiopharmaceuticals

Table 1 : Radiation dose received during eluting the generator

S. No	Activity eluted (MBq)	Activity eluted (mCi)	Total duration for elution (mins)	Radiation dose (μSv)
1	6993	189	8	16
2	6475	175	8	15
3	6068	164	7	15
4	5550	150	6	14
5	5402	146	7	14
6	4921	133	8	12
7	4477	121	9	13
8	3774	102	6	11
9	3626	98	9	11
10	3071	83	8	9
11	2442	66	8	8
12	1998	54	9	9
13	1295	35	9	7
Mean	4314.76	116.78	7.92	11.5
Std dev	1787.04	51.27	1.07	3.10

Table 2: Radiation exposure during the labeling of 188Re-Lipiodol

S. No	Activity used (MBq)	Activity used (mCi)	Total duration of RP synthesis (mins)	Radiation dose (μSv)
1	4440	120	90	57
2	4033	109	86	46
3	3552	96	102	55
4	3774	102	88	45
5	3256	88	95	47
6	3182	86	100	48
Mean	3706.16	103	95	52.50
Std dev	479.81	12.04	7.07	6.36

Table 3: Radiation exposure during the labeling of 188Re-HEDP

S. No	Activity used (MBq)	Activity used (mCi)	Total duration of RP synthesis (mins)	Radiation dose (μSv)
1	3774	102	41	12
2	3626	98	37	8
3	3256	88	44	7
4	2812	76	38	6
Mean	3367	89	40	9
Std dev	429.27	11.6	2.12	4.24

Table 4: Radiation exposure during the labeling of 188Re-Tin colloid

S. No	Activity used (MBq)	Activity used (mCi)	Total duration of RP synthesis	Radiation dose (μSv)
1	1295	35	131	5
2	1110	30	129	4
3	962	26	134	3
Mean	1122.33	30.50	131.50	4
Std dev	166.84	6.36	2.12	1.41

mSv, followed by ^{188}Re-HEDP of 0.009 ± 0.002 mSv, whereas the dose from the labeling of ^{188}Re-Tin colloid was the lowest 0.004 ± 0.0006 mSv. It was observed that the time for which the activity manipulation was done with the hands was highest for ^{188}Re-Lipiodol followed by the same time for ^{188}Re-HEDP and ^{188}Re-Tin colloid. Furthermore, the highest amount of activity was handled for ^{188}Re-Lipiodol followed by ^{188}Re-HEDP and the lowest for ^{188}Re-Tin colloid. The two parameters which were found crucial for the observed trend were the time for which the

radioactivity is handled and amount of the activity handled during the radiolabelling procedures. Higher the both, higher is the radiation exposure**.** Furthermore, the doses received by the radiopharmacist were higher during elution. The activity eluted in the initial days was higher than on the days nearing the end of shelf life as is observed with other generator systems.

Another parameter that could be crucial for the dose received by the occupational worker is how proficient or dexterous is the radiopharmacist in handling the radioactivity.[4] The doses can be different for different workers depending on the level of their expertise to handle radioactivity. In this study, it was ensured that only the trained staff was involved and also, all the labeling procedures were carried by the single radiopharmacist to minimize the interpersonnel differences. Same pocket dosimeter was assigned every time during the labeling procedure to rule out the error from different devices.

The mean whole-body dose received by the radiopharmacistin thirteen radiolabeling procedures (Lipiodol-6, HEDP-4, Tin colloid-3) was found to be 0.025 mSv in 6 months. This dose received by a single radiopharmacist, over a period of 6 months at the current frequency was far below the occupational limits. However, the total dose received by the radiopharmacist in handling a total of 56 GBq in all the 13 synthesis of the three radiopharmaceuticals was 0.786 mSv. These results leave us with greater flexibility to handle much higher activity for much longer time. If we assume double the number of synthesis per 6 months (24 synthesis/year) and that too of ^{188}Re-Lipiodol, since the highest mean exposure (0.052 mSv) was obtained during the synthesis of ^{188}Re-HDD/Lipiodol, the doses to the personnel involved in a year will be 1.248 mSv. The readings of the chest TLD badge and the wrist TLD badge of the worker for the cumulative Re-188 radiopharmacy as well as the other departmental work during this period of 6 months was 0.5 mSv and 0.6 mSv, respectively. This reading was well within the permissible limits and insignificantly higher to the doses received by the worker with routine departmental work alone. Although the doses received were far below the limits, the radiation workers were advised to follow ALARA principle and it was suggested that trained occupational workers should work on rotation.[5]

The regular use of radiation monitoring devices such as the pocket dosimeters and TLD badges was encouraged, and radiation surveys were conducted routinely in the department.

The present study has certain limitations. First, we measured whole-body doses in regard to Re-188 manipulation but could not measure the extremity doses. Second, a small number of whole-body measurements could be taken due to the limited number of patients were available during the shelf life of the generator.

Conclusion

This study confirmed that the synthesis of ^{188}Re-radiopharmacy is safe and the whole-body radiation doses received by personnel involved in the radio-labeling procedures were within recommended safety levels of occupational dose limits of AERB, i.e., 20 mSv/year (averaged over 5 years).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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