Title	Administered dosage and effective dose estimated from ^{81}Rb-rubidium hydroxide for lung ventilation scintigraphy using ^{81m}Kr noble gas
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Title: Administered dosage and effective dose estimated from ^{81}Rb-rubidium hydroxide for lung ventilation scintigraphy using ^{81m}Kr noble gas.

(Short title: Dose estimation using ^{81m}Kr gas.)

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Abstract

The aim of this study was to estimate the administered dosage of ^{81m}Kr noble gas as calculated by the radioactivity of ^{81}Rb-rubidium hydroxide (^{81}RbOH). The administered dosage was regarded as the total amount of ^{81m}Kr noble gas. The radioactivity of ^{81m}Kr was calculated using the radioactivity of ^{81}RbOH at the examination, the beginning of inhalation, the inhalation duration, and the attenuation volume from the generator to the patient for ^{81m}Kr noble gas. In addition, we created an Internet survey and asked National University Hospital in Japan to respond to questions regarding the parameters of concern. Survey responses were provided by 38 hospitals (response rate was 90.5%). Twenty-seven hospitals (64.3%) examined lung ventilation scintigraphy using ^{81m}Kr noble gas. The mean administered dosage and the effective dose of lung ventilation scintigraphy using ^{81m}Kr noble gas were 35.8 ± 22.1 GBq and 0.97 ± 0.60 mSv, respectively.

Key Words: lung ventilation scintigraphy, ^{81m}Kr noble gas, ^{81}RbOH, administered dosage, effective dose,

INTRODUCTION

Lung ventilation scintigraphy is useful for evaluating local pulmonary function and for diagnosing pulmonary thromboembolism(1-5), obstructive pulmonary disease(6,7), pulmonary hypertension(8-10) and lung transplantation(11,12). For lung ventilation scintigraphy, inert radioactive noble gases (^{133}Xe and ^{81m}Kr) can be used. On inhalation, the radiopharmaceutical is distributed to the lungs according to the local lung ventilatory capacity and is excreted in the exhaled air, thus allowing the ventilation capacity of the lungs to be examined. To acquire lung ventilation scintigraphy, the subject must inhale continuously during scanning. Consequently, the radioactivity of ^{81m}Kr noble gas cannot be measured prior the examination. In addition, because the physical half-life of ^{81m}Kr is as short as 13 seconds, direct measurement is difficult.

In Japan, the partial revision of the Ordinance for the Enforcement of the Medical Care Act came into effect in April 2020, establishing a safety management system for medical radiation. As a result, it has become compulsory for each facility to manage and record the radiation dose for each examination. The administered dosage of lung ventilation scintigraphy is excluded at diagnostic reference levels (DRLs) from various countries(13-17). According to the Japan DRLs 2020(18), the DRLs for pulmonary ventilation scintigraphy using ^{81m}Kr gas was 200 MBq. Since this value is considered to be the radioactivity of the parent nuclide, ^{81}Rb-rubidium hydroxide (^{81}RbOH), it is impossible to evaluate the administered dosage of ^{81m}Kr gas during each examination. For most examinations using liquid radiopharmaceuticals, the actual dose can be measured using a dose calibrator and then easily recorded. However, for lung ventilation scintigraphy using ^{81}Rb-^{81m}Kr generator, continuous inhalation is needed to acquire planar or single photon emission computed tomography (SPECT) images. As mentioned above, measuring the actual administered dosage for lung ventilation scintigraphy using ^{81m}Kr noble gas is difficult.

On the other hand, because ^{81m}Kr ($T_{1/2}$ =13 seconds) is in transient equilibrium with ^{81}Rb ($T_{1/2}$ = 4.6 hours) during continuous inhalation, the radioactivity of ^{81m}Kr noble gas can be estimated based on calculation using ^{81}RbOH at the time of examination. The administered dosage of lung ventilation scintigraphy is estimated by adding the total amount of radioactivity from start to finish. The primary aim of this study was to estimate the administered dosage of lung ventilation scintigraphy using ^{81m}Kr noble gas. Furthermore, we compared the administered dosages among National University Hospitals in Japan.

MATERIALS AND METHODS

Calculation method of integrated ^{81m}Kr dosage

The schema for the ^{81}Rb-^{81m}Kr generator and delivery system is shown in Figure 1. The radioactivity (A_{Kr}) of ^{81m}Kr can be estimated eq. (1) as follows:

$$A_{Kr}(t) = kA'_{Kr}(t) \quad (1)$$

where $A_{Kr}(t)$ is the radioactivity of ^{81m}Kr at patient inhalation,

$A'_{Kr}(t)$is the radioactivity of ^{81m}Kr at the ^{81}Rb-^{81m}Kr generator, and

k is the decay ratio from the ^{81}Rb-^{81m}Kr generator to patient.

The half-life of ^{81m}Kr is 13 seconds, which is shorter than the that of ^{81}Rb (4.6 hours), so the equation for the transient equilibrium state holds. Because ^{81m}Kr is a daughter nuclide from ^{81}Rb, the radioactivity of ^{81}Rb and ^{81m}Kr can be estimated by eq. (2) and (3) as follows:

$$A'_{Rb}(t) = A_{Rb}\exp(-\lambda_{Rb}(t - t_0)) \quad (2), \text{ and}$$

$$dA'_{\mathrm{Kr}}(t)/dt = \lambda_{Rb}A'_{Rb}(t) - \lambda_{Kr}A'_{Kr}(t) \quad (3),$$

where A_{Rb} is the certified radioactivity of ^{81}RbOH (in MBq),

A'_{Rb} is the radioactivity of ^{81}RbOH at the examination (in MBq),

t_0 is the certification time of ^{81}RbOH,

λ_{Rb} is the decay constant of ^{81}Rb (sec^{-1}), and

λ_{Kr} is the decay constant of ^{81m}Kr (sec^{-1}).

If the generated activity $A'_{Kr}(t)$ is completely flushed with oxygen gas into the generator, the second term of eq(3) ceases to exist. Hence, eq (2) and (3) can be transformed into eq(4) as follows:

$$dA'_{\mathrm{Kr}}(t)/dt = \lambda_{Rb} A'_{Rb}(t) = \lambda_{Rb} A_{Rb} \exp\left(-\lambda_{Rb}(t - t_0)\right) \qquad (4).$$

The administered dosage of lung ventilation scintigraphy, A_{total} can thus be estimated by adding up the amount of radioactivity.

$$A_{total} = \int_{t_s}^{t_f} A_{Kr}(t)dt = \int_{t_s}^{t_f} k\lambda_{Kr} A'_{Kr}(t)dt = \int_{t_s}^{t_f} k\lambda_{Kr}\lambda_{Rb} A'_{Rb}(t)dt \qquad (5),$$

where A_{total} is the administered dosage of lung ventilation scintigraphy,

t_s is the start time of inhalation and

t_f is the finish time of inhalation.

According to eq(5) and Figure 1, the decay ratio of k is estimated by the volume of delivery system and the flow rate:

$$k = \exp\left(-\lambda_{Kr}(V_G + V_T)/F\right) \quad (6),$$

where V_G is the volume of ^{81}Rb-^{81m}Kr generator,

V_T is the summed volume of the tube from the ^{81}Rb-^{81m}Kr generator to the patient, and

F is the flow velocity of ^{81m}Kr noble gas (= O_2 gas).

In Japan, only one supplier of ^{81}Rb-^{81m}Kr generators with insurance approval is available and the certification time is 2 P.M. The parameters t_s and t_f were set to the start time of the first acquisition and the finish time of the last acquisition, respectively. As mentioned above, the total activity of lung ventilation scintigraphy is integrated from time t_s to time t_f and can be estimated by eq. (7):

$$A_{total} = \int_{t_s}^{t_f} k\,\lambda_{Kr}\,\lambda_{Rb} A'_{Rb}(t)dt = \frac{\exp\left(-\lambda_{Kr}(V_G + V_T)/F\right)\lambda_{Kr}A_{\mathrm{Rb}}[\exp\left(-\lambda_{Rb}(t_s - t_0)\right) - \exp\left(-\lambda_{Rb}(t_f - t_0)\right)]}{\lambda_{Rb}}$$

(7).

The variable parameters are the certified radioactivity of ^{81}RbOH, the start and finish inhalation times, the flow velocity from the ^{81}Rb-^{81m}Kr generator to the patient, and the summed volume of the tube (A_{Rb}, t_s, t_f, F and V_T respectively).

Data collection and analysis

We created an Internet survey form and asked each facility to provide responses for each parameter. The parameters included on the survey form were the certified activity of ^{81}RbOH, the start and finish inhalation times, the flow velocity, and the volume from the ^{81}Rb-^{81m}Kr generator to the patient. All the parameters were obtained from each facility between August and December 2021. The effective dose was also estimated the conversion coefficient, 2.7 × 10^{-5} mSv/MBq, specified in ICRP publication 53[(19)]. This study was approved by the Research Ethics Board of Chiba University (Approval no. 735) and Osaka University Hospital (Approval no. 21220).

RESULTS

Table 1 showed the results of the survey form. Of the 42 university hospitals in Japan, 27 facilities (64.3%) perform lung ventilation scintigraphy using ^{81m}Kr noble gas. Seven facilities (25.9%) perform planar acquisition only, and another facility (3.7%) performs SPECT acquisition only. Five facilities (18.5%) receiving 370 MBq acquired both planar and SPECT images. Table 2 and Table 3 shows comparisons between planar only and combined planar and SPECT scans. The scans at the planar-only facilities were performed in all eight directions. The mean administered dosages of all, planar only and planar with SPECT facilities were 35.8 ± 22.1, 30.2 ± 16.4 and 39.1 ± 23.8 GBq, respectively. The mean effective doses of those were 0.97 ± 0.60, 0.82 ± 0.44 and 1.06 ± 0.64 mSv, respectively.

DISCUSSION

To the best of our knowledge, this is the first report to estimate the administered dosage and the effective dose of lung ventilation scintigraphy using ^{81m}Kr noble gas at multiple facilities. The mean administered dosage was 35.8 ± 22.1 GBq. This is a very large value. Dudley et al. reported the administered activity of ^{81m}Kr for simultaneous planar imaging using ^{99m}Tc-MAA[(20)]. They estimated a value of 2.5 ± 1.9 GBq (the maximum dosage was 6.1 GBq). Because only planar images were acquired, the administered dosage in this study was higher than this previous reported value. Because of a UK nuclear medicine survey conducted in 2003-2004[(21)], the DRLs published by the Administration of Radioactive Substances Advisory Committee was 6.0 GBq. However, they did not ask for the administered activity because of the difficulty in actually estimating this value. Because only planar images were typically acquired during lung perfusion scintigraphy examinations performed at that time, this situation was considered to be similar for lung ventilation scintigraphy. In the present survey, however there were 13 facilities (48.1%) that performed SPECT/CT scans in addition to collecting planar images. Hybrid SPECT/CT scanners can provide information on lung perfusion and ventilation, compared with diagnostic CT images alone[(1)]. In addition, all the facilities that performed only planar acquisition were obtained images in all eight directions. The addition of multi-direction planar or SPECT acquisition necessarily increases the duration of inhalation.

According to this study, the administered dosage of ^{81m}Kr gas was calculated using the certified radioactivity of ^{81}RbOH, the start time of inhalation, the inhalation duration, and the attenuation volume from the ^{81}Rb-^{81m}Kr generator to the patient. The certified radioactivity of ^{81}RbOH is available in Japan for two values: 185 or 370 MBq. The mean value of ^{81}RbOH was 219 ± 73.2 MBq in the present study. This value was close to the 200 MBq mentioned by the Japan DRLs 2020(18). The inhalation duration depended on the number of directions used for planar images and whether SPECT acquisition was additionally performed. According to the results, SPECT acquisition was performed in 20 facilities (74.1%). Lung ventilation SPECT imaging reportedly improves diagnostic performance, compared to planar images(22-26). As with lung perfusion SPECT images, the SPECT images of lung ventilation are expected to improve the detection of ventilatory disturbances, compared with planar images, and to have the advantage of being comparable to CT images. From a previous survey of nuclear medicine practices in Japan, the ratio with additional SPECT acquisition increased to 49.6% in 2017 from 28.6% in 2012(27). In recent years, some societies have republished their guidelines for the treatment of pulmonary hypertension(28, 29). With the widespread installation of

SPECT/CT scanners, the results of this study suggest a higher ratio.

We estimated the administered dosage by calculating the integral activity under equilibrium between flow velocity and the generation of ^{81m}Kr. We did not consider the initial radioactivity of ^{81m}Kr. Kato et al. reported the kinetics (flow rate and radioactivity) of ^{81}Rb-^{81m}Kr generators[30]. The volume of the generator was 1.3 mL, so the radioactivity of ^{81m}Kr was reported to reach equilibrium within 1 second after the maximum value. Since the initial dosage of the ^{81}Rb-^{81m}Kr generator was 185 or 370 MBq, which was low compared with the integral inhalation activity, and given the rapid transition to the equilibrium state, the results of this study show an effect that was smaller than the total activity.

The flow rates were from 0.5 to 3.0 L/min, in compliance with the speed described in the attached document. The summed volume of the tube from the generator to the patient was highly variable (between 7.4 to 133.1 mL). The length of the tube was determined at each facility so as to ensure safety, taking the movement of the scanning table into consideration. As a result of these parameters, flow rates and summed volumes, the greatest attenuation ratio for the tube was 69.1%.

We estimated the effective dose using ICRP publication 53[19]. ICRP publication 53 mentioned that this factor may overestimate the absorbed dosage to the lungs because the administered activity is assumed to be retained in the lungs with an effective half-life equal to the physical half-life (13 seconds). In fact, the inhaled volume may not be sufficient in patients with lung disease. According to the conversion coefficient of 1.1×10^{-2} mSv/MBq in ICRP publication 128 for ^{99m}Tc-labeled macro-aggregated albumin (^{99m}Tc-MAA)[31], the effective dose absorbed by 260 MBq of ^{99m}Tc-MAA is 2.86 mSv, as mentioned in Japan DRLs 2020[18]. The third quartile dosage of lung ventilation scintigraphy using ^{81m}Kr noble gas was 48.5 GBq in the present study. The effective dose was 1.31 mSv, which was lower than that of ^{99m}Tc-MAA. If this method is used in the next survey for Japanese DRLs, it may be possible to obtain comparable values for each facility.

CONCLUSION

This study showed that the administered dosage of lung ventilation scintigraphy using ^{81m}Kr noble gas could be calculated using the certified radioactivity of ^{81}RbOH, the start time of inhalation, the inhalation duration, the flow velocity from the ^{81}Rb-^{81m}Kr generator to the patient, and the summed volume of the tube. The average administered dosage and the effective dose were 35.8 ± 22.1 GBq and 0.97 ± 0.60 mSv, respectively.

Despite the numerous administered dosages in use, the effective dose of lung ventilation scintigraphy using ^{81m}Kr noble gas was smaller than that of lung perfusion scintigraphy. This methodology successfully evaluated administered dose and can be used by others to do the same at their nuclear medicine facilities.

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FIGURE LEGENDS

Fig. 1 Overview of ^{81}Rb-^{81m}Kr generator and delivery system for lung ventilation scintigraphy.

The administered dosage of lung ventilation scintigraphy is the integrated activity during the inhalation of ^{81m}Kr noble gas. Inhalation radioactivity to patient, $A_{Kr}(t)$, was calculated by considering the radioactivity of the ^{81}Rb-^{81m}Kr generator, $A'_{Rb}(t)$ and $A'_{Kr}(t)$, and correcting for the decay during delivery from the generator to the patient. The decay factor is decided by flow velocity and the volume of the delivery system.

Table 1 Survey results from National University Hospital in Japan

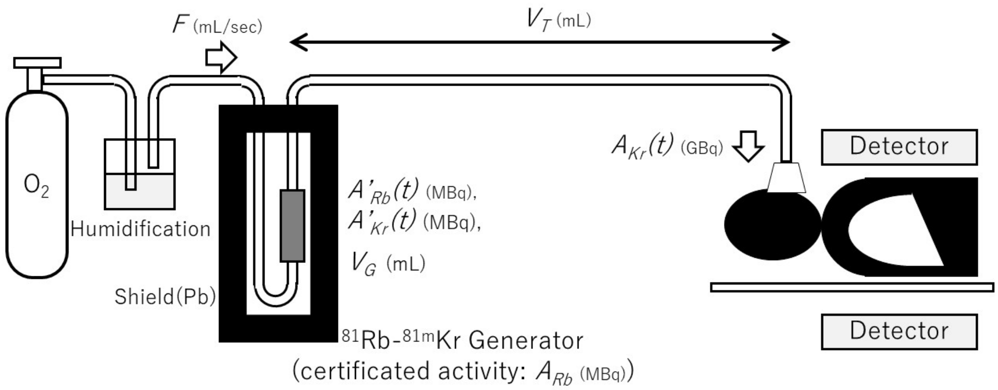
Number of facilities	
Provided survey	42
Response	38
Examination of lung ventilation scintigraphy using ^{81m}Kr	27
Acquisition method	
Planar only	7
SPECT only	1
Planar with SPECT	6
Planar with SPECT/CT	13
Certified dose of $^{81}RbOH$	
185 MBq	22
370 MBq	5
Mean (MBq)	219.3 ± 73.2

Table 2 Parameters of lung ventilation scintigraphy using ^{81m}Kr noble gas

	Total	Planar only	Planar with SPECT
Number of facilities	27	7	19
Certified dose of $^{81}RbOH$ (MBq)			
Minimum	185	185	185
Mean	219.3 ± 73.2	185.0 ± 0.0	233.3 ± 83.4
Maximum	370	185	370
Direction number of planar images			
Minimum	0	8	2
Mean	5.5 ± 2.7	8.0 ± 0.0	5.8 ± 2.5
Maximum	8	8	8
Start inhalation time (hh:mm:ss)			
Earliest	9:00:00	9:00:00	9:20:00
Mean	10:39:27	9:55:00	10:48:25
Latest	15:30:00	11:10:00	15:30:00
Duration of inhalation (min)			
Shortest	20.0	20.0	20.0
Mean	33.3 ± 13.2	30.0 ± 14.1	35.2 ± 12.9
Longest	60.0	60.0	60.0
Radioactivity of $^{81}RbOH$ at start time (MBq)			
Minimum	147.4	284.2	147.4
Mean	379.4 ± 165.2	347.2 ± 54.8	399.8 ± 189.9
Maximum	731.5	394.5	731.5
Flow velocity (L/min)			
Minimum	0.5	1.5	0.5
Mean	2.0 ± 0.8	2.1 ± 0.5	1.9 ± 0.9
Maximum	3.0	3.0	3.0
Summed volume of tube (mL)			
Minimum	7.4	7.4	7.4
Mean	40.3 ± 38.4	49.1 ± 47.1	37.6 ± 36.7
Maximum	133.1	129.1	133.1

Table 3 Administered dose and effective dose of lung ventilation scintigraphy using ^{81m}Kr noble gas

	Total	Planar only	Planar with SPECT
Administered dose (GBq)			
Minimum	12.9	14.7	13.4
Median	30.6	25.4	32.4
Third quartile	48.5	34.6	48.6
Maximum	113.0	63.7	113.0
Mean	35.8 ± 22.1	30.2 ± 16.4	39.1 ± 23.8
Effective dose (mSv)			
Minimum	0.35	0.40	0.36
Median	0.83	0.69	0.88
Third quartile	1.31	0.93	1.31
Maximum	3.05	1.72	3.05
Mean	0.97± 0.60	0.82 ± 0.44	1.06 ± 0.64



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Summed volume of tube (mL)			
Minimum	7.4	7.4	7.4
Mean	40.3 ± 38.4	49.1 ± 47.1	37.6 ± 36.7
Maximum	133.1	129.1	133.1

Table 3 Administered dose and effective dose of lung ventilation scintigraphy using ^{81m}Kr noble gas

	Total	Planar only	Planar with SPECT
Administered dose (GBq)			
Minimum	12.9	14.7	13.4
Median	30.6	25.4	32.4
Third quartile	48.5	34.6	48.6
Maximum	113.0	63.7	113.0
Mean	35.8 ± 22.1	30.2 ± 16.4	39.1 ± 23.8
Effective dose (mSv)			
Minimum	0.35	0.40	0.36
Median	0.83	0.69	0.88
Third quartile	1.31	0.93	1.31
Maximum	3.05	1.72	3.05
Mean	0.97± 0.60	0.82 ± 0.44	1.06 ± 0.64