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Biological Half-Life of Technetium-99m Ethambutol in Tuberculosis Patients: A Whole-Body Scan Perspective

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Abstract

The development of an etambutol radiopharmaceutical kit by Center for Nuclear Material and Radiometry Technology (PTNBR) Batan aims to enhance the specificity of Mycobacterium Tuberculosis (MTb) imaging, as causative agent of tuberculosis. This research evaluates the distribution and biological half-life of Technetium-99m Ethambutol radiopharmaceutical in the lungs, right kidney, left kidney, and bladder. This information is crucial for understanding the radiopharmaceutical's distribution within the body and improving the interpretation of whole-body etambutol scan results. The region of interest (ROI) technique was employed to delineate the areas of interest in the anterior and posterior images. The study sample consisted of 20 patients suspected of TB, with 9 females and 11 males aged 19 to 75 years. The results demonstrated that Technetium-99m Ethambutol was distributed throughout the body with primary excretion routes through urine and feces. The highest activity was observed in the lungs, indicating the presence of tuberculosis infection. The longest biological half-life of Technetium-99m Ethambutol was recorded in the left kidney (6.51 ± 2.53 hour) with a decay constant of 0.235 $hour^{-1}$ and the right kidney (5.40 ± 2.02 hour) with a decay constant of 0.261 $hour^{-1}$.

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INTRODUCTION

After the 2019 coronavirus pandemic, tuberculosis was declared the second leading cause of death, with 1.3 million fatalities in 2022 (World Health Organization, 2023). Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (MTb), which more commonly affects adults (World Health Organization, 2023). This bacterial infection can affect the lungs, known as pulmonary tuberculosis, or other organs such as bones, lymph nodes, joints, and intestines, referred to as extrapulmonary tuberculosis (Roselliana et al., 2019). The primary transmission of TB occurs through airborne droplets expelled by active patients when they cough, sneeze, or talk. At certain times, the bacteria in the lungs can become active and cause various health problems. Factors such as HIV, malnutrition, diabetes, and long-term use of immunosuppressive or corticosteroid medications can exacerbate the infection (Ait-Khaled & Enarson, 2003).

As a diagnostic method, nuclear medicine offers a rapid, non-invasive examination to diagnose pathophysiological and pathobiochemical changes at an early stage. Various available radiopharmaceuticals are introduced into biological mediums to produce anatomical-functional images of the body based on the interaction of the pharmaceuticals and radioactive decay. However, challenges in diagnosing tuberculosis remain, such as the difficulty in localizing extrapulmonary tuberculosis and differentiating between various Mycobacterium species (Roselliana et al., 2019). Therefore, in 2018, Indonesian researchers developed the radiopharmaceutical Technetium-99m Ethambutol. Etambutol, an antitubercular antibiotic, acts as a targeting agent, specifically binding to the mycolic acid in the cell wall of Mycobacterium tuberculosis, the causative agent of tuberculosis. This targeted binding allows for the visualization and localization of tuberculous lesions using nuclear imaging techniques.

Research by Kartamihardja et al. (2018) involving 168 TB patients showed that Technetium-99m Ethambutol had a sensitivity and specificity of 94.9% and 83.3%, respectively, in detecting tuberculosis. However, the available research is still very limited. This study focuses on analyzing the biological half-life of Technetium-99m Ethambutol in the critical organs such as lungs, bladder, right and left kidneys, in tuberculosis patients. This will provide information on the elimination rate of the radiopharmaceutical from organs due to metabolic processes occurring within the body.

METHOD

This research utilized retrospective data from 20 suspected TB patients, encompassing both pulmonary and extrapulmonary TB cases. The sample consisted of both male and female individuals, with no age distinctions, who received radiopharmaceutical accumulation in the lungs, right kidney, left kidney, and bladder. All samples received technetium-99m ethambutol injections and underwent examinations twice, at one- and four-hours post-injection. The obtained data comprised anterior and posterior images from each examination. Organ delineation was performed using region of interest (ROI) techniques for the lungs and bladder against the anterior images, while delineation for the right and left kidneys was conducted on the posterior images.

The delineation results were in the form of radioactivity counts accumulated in the organs under investigation. Data processing proceeded through several stages as follows:

1. Converting counts to millicurie units to obtain the total accumulated radioactivity dose in each organ for the first and second examinations. The calculation was performed using Equation (1).

$$A\ (mCi) = \frac{Count}{Duration\ of\ Examination} \times Correction\ Factor \quad (1)$$

where count obtained from organ delineation, the ethambutol examination time being 15 minutes, and the correction factor (cpm/mCi) derived from counting 1 mCi of Technetium-99m at a distance of 7 cm from the gamma camera detector face.

2. Calculating the biological half-life using Equation (2) based on the activity of each organ (Desita et al., 2017).

$$T_B = -\frac{0.693}{ln\frac{A_t}{A_0}}\Delta t \quad (2)$$

where At is the organ activity at the second examination, A0 is the organ activity at the first examination, and Δt is the interval between examinations 1 and 2 (3 hours).

3. Determining the decay constant using Equation (3) to assess the radioactivity decay rate in each organ (Desita et al., 2017; Tunggadewi et al., 2022)

$$\lambda = \frac{0.693}{T_E} \quad (3)$$

where TE is the effective half-life or total half-life.

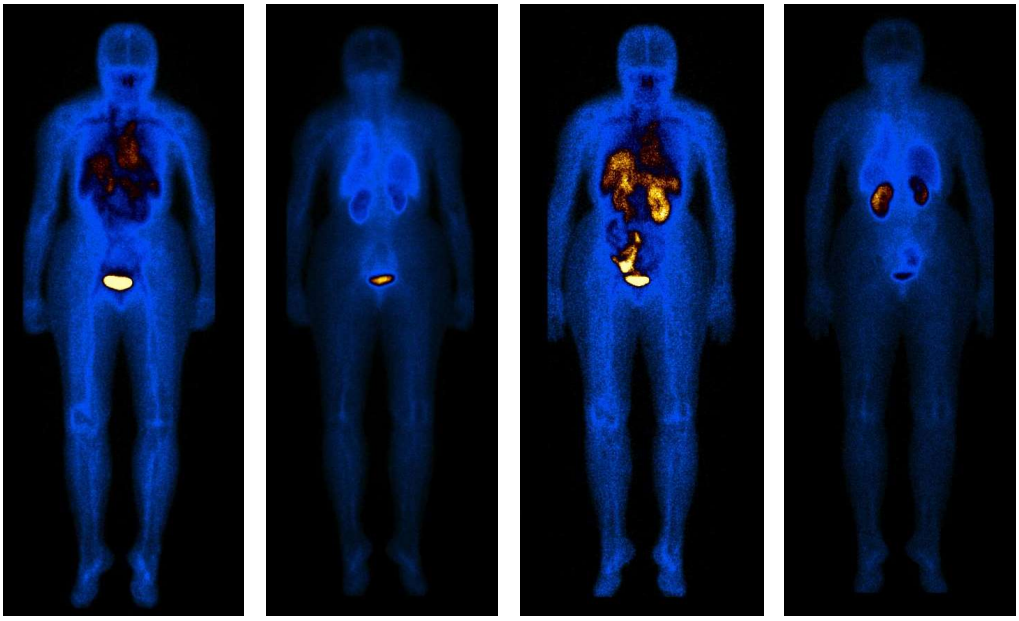
RESULT AND DISCUSSION

The study involved 20 suspected tuberculosis patients, comprising 9 females (45%) and 11 males (55%), with ages ranging from 19 to 75 years. Based on this, tuberculosis infection predominantly affects adult patients (≥ 40 years) and males compared to other age and gender groups. This data is consistent with the Global Tuberculosis Report 2023, which indicates that 90% of tuberculosis patients are aged over 15 years, and 50% are male (World Health Organization, 2023). A study by Nurjana (2015) elucidated various factors contributing to the increased incidence of tuberculosis among individuals of working age, including high frequency of outdoor activities, poverty, living conditions, and unhealthy lifestyles due to smoking.

Tuberculosis screening commenced with the administration of 15 mCi Technetium-99m ethambutol intravenously. Subsequently, patients underwent dual-head gamma camera scanning for 15 minutes at one- and four-hours post-injection. During the waiting period, patients were instructed to consume water to maximize the distribution of radiopharmaceuticals to the examination target and throughout the body (Tunggadewi et al., 2022). The resulting images will visualize the spread of tuberculosis bacteria and the biodistribution of Technetium-99m Ethambutol.

Activity of Technetium-99m Ethambutol

The radiopharmaceutical technetium-99m ethambutol that enters the body will bind to plasma proteins and disseminate through the bloodstream. According to Roselliana et al. (2019), radiopharmaceuticals administered via intravenous injection will target Mycobacterium tuberculosis bacteria located deep within the body. The distribution of technetium-99m ethambutol, as stated by Dollery & Boobis (1999), is reported to be similar to unlabeled ethambutol. Based on the results of the entire series of scans, accumulation of radiopharmaceuticals was detected in various organs, including the lungs, bones (in some patients), liver, gallbladder, intestines, kidneys, bladder, and several other organs, as depicted in Figure 1.



(a) (b) (c) (d)

Figure 1. The biodistribution at 1-hour anterior (a) and posterior (b), and 4-hour anterior (c) and posterior (d).

The presence of activity in the urinary and hepatobiliary systems indicates that technetium-99m ethambutol is excreted from the body through urine and feces, as concluded by the studies of Khurana et al. (2022) and Kartamihardja et al. (2018). This finding is further supported by the explanation provided by Drugbank (2024) which indicates that 50% of the radiopharmaceutical is eliminated through urine in the form of the main compound, 8-15% as inactive metabolites, and 20-22% is excreted through feces. Additionally, approximately 10% to 50% of extrapulmonary tuberculosis cases show lung infection (Lee, 2015). Therefore, this research identifies the lungs as the target organ for infection and the kidneys and bladder as the excretory organs.

The calculation of radiopharmaceutical activity in each organ is based on the count values obtained from the ROI delineation, as shown in Figure 2.

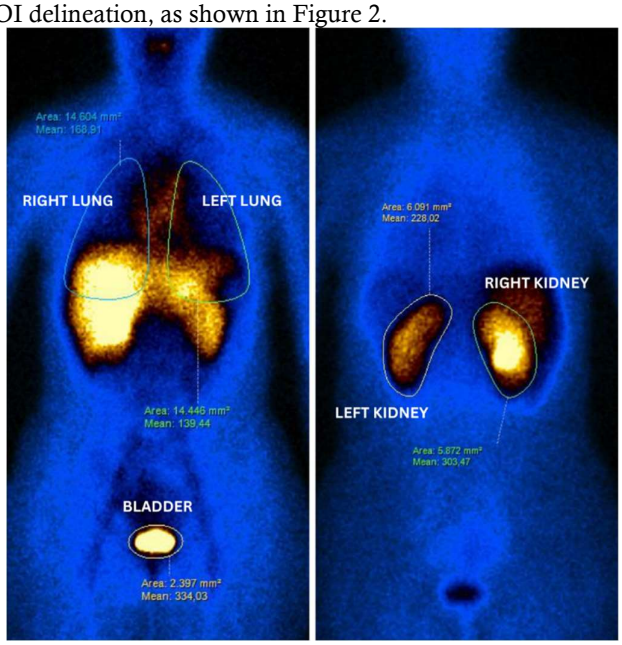


Figure 2. Example of Count Measurement Results in Lungs, Bladder, and Kidneys.

The count values are then converted into activity units (mCi) using a conversion factor of 0.000003466 mCi/cpm. The results of the calculations indicate that each organ accumulates differently. Additionally, patient compliance with water intake and the duration of the waiting period affect the amount of radiopharmaceuticals eliminated from the body. Table 1 presents the average activities in the first and second scans.

Table 1. Average Activity of Technetium-99m Ethambutol in Organs

Organ	Mean ± SD (mCi)	
	Scan 1	Scan 2
Lungs	0.74 ± 0.18	0.38 ± 0.10
Right Kidney	0.28 ± 0.10	0.18 ± 0.07
Left Kidney	0.23 ± 0.07	0.16 ± 0.05
Bladder	0.55 ± 0.53	0.18 ± 0.19

The activity data from the first and second examinations in Table 1 indicate that the lungs have the highest average activity level, followed by the bladder, right kidney, and left kidney. The high accumulation of radiopharmaceuticals in the lungs indicates the possibility of tuberculosis bacterial infection in that organ. However, to confirm the diagnosis, further examinations such as sputum tests or chest X-rays are required. Additionally, the research results show higher activity accumulation in the right kidney compared to the left kidney, contrary to the findings of Desita et al. (2017) and Ni'amah et al. (2017). This difference is attributed to the overlap between the right kidney and the gallbladder and disorders in the right kidney (Desita et al., 2017). There is also a relatively high accumulation in the bladder due to the absence of voiding before the examination, causing the detector to capture a lot of radiation from contaminated urine.

Biological Half-Life of Technetium-99m Ethambutol

The biological half-life represents the time required for the radiopharmaceutical's activity to decrease to half of its initial value. In this study, the calculation was performed using the organ activity values from the first and second examinations. Additionally, the decay constant was determined to indicate the rate of radiopharmaceutical decay, which can explain the obtained biological half-life results. The calculation results reveal differences in the biological half-life and decay constant among the organs studied, as recorded in Table 2.

Table 2. Average Half-Life and Decay Constants

Organ	Biological Half-Life (Hours)	TotalHalf-Life (Hours)	Decay Constant ($Hour^{-1}$)
Lungs	3.19 ± 0.62	2.07 ± 0.27	0.341
Right Kidney	5.40 ± 2.02	2.76 ± 0.52	0.261
Left Kidney	6.51 ± 2.53	3.03 ± 0.49	0.235
Bladder	2.56 ± 1.43	1.69 ± 0.68	0.503

Table 2 shows that the left and right kidneys have longer biological half-lives compared to the lungs and bladder. This indicates that the right and left kidneys decay at a slower rate. This is evidenced by the decay constant values obtained, which are 0.235 hour-1 for the left kidney and 0.261 hour-1 for the right kidney. Consequently, the right and left kidneys retain the radiopharmaceuticals for a longer period, leading to increased radiation exposure to the surrounding organs. According to a report from Valeant Canada LP (2018), ethambutol is eliminated from the body within 3.3 hours in

patients with normal kidney function, and in 7 hours or more in patients with impaired kidney function.

Based on the organ activity values in Table 1, organs with initially low radiopharmaceutical uptake and only a slight decrease in activity during the second examination have a long biological half-life. The variation in decay constants indicates how quickly or slowly the radiopharmaceutical activity in an organ decay over a specific period. It is evident that the smaller the decay constant, the longer the resulting biological half-life. These findings are consistent with the studies by Mutohar et al. (2017) and Tunggadewi et al. (2022), which demonstrate an inverse relationship between half-life and decay constant.

Andrade (2022) stated that any factors affecting distribution, metabolism, and excretion will increase the biological half-life. These influencing factors include kidney health conditions, age, nutrition, medication use, elimination of radiopharmaceuticals from the body through urine and sweat, and other medical histories (Andrade, 2022). The more water a patient consumes, the more frequent the elimination process occurs, leading to a greater amount of radiopharmaceuticals being expelled from the body. Conversely, patients with impairments in certain organs tend to retain radiopharmaceuticals longer due to suboptimal metabolism. Furthermore, the efficiency of kidney function and other excretory organs also plays a crucial role in determining how quickly radiopharmaceuticals can be eliminated.

CONCLUSION

This study reveals that Technetium-99m Ethambutol is eliminated from the body over a specific period, depending on the amount of water consumed and any organ impairments. In this study, the kidneys exhibited a longer biological half-life compared to the lungs and bladder, indicating that the decay rate of the radiopharmaceutical in the kidneys is slower. Additionally, it was found that the relationship between biological half-life and decay constant is non-linear. Factors such as the ability to eliminate radiopharmaceuticals through urinary and sweat excretion mechanisms, as well as the health conditions of the patient's organs, can influence both the half-life and the decay constant.

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