Role of Radiopharmaceuticals in the Management of Tuberculosis

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This chapter significantly defines Tuberculosis (TB) as an infectious disease caused by mycobacterium tuberculosis bacillus. M. Tuberculosis is rod-like in shape, highly aerobic and it requires high levels of oxygen. It's a serious illness which mainly affects the mammalian respiratory system. Tuberculosis (TB) remains a global health challenge, requiring continuous efforts to improve diagnostic accuracy and treatment outcomes. It can spread very rapidly from one infected person to uninfected person however the dividing rate of the bacteria is much slower than other bacteria. TB can be categorized as being active or latent. Active TB is more contagious, and it causes symptoms where latent TB on the other hand doesn't cause any sort of symptoms and is not contagious. The general symptoms being seen in active TB infection are fever, cough, chills, weight loss, fatigue, loss of appetite etc. If a person is infected with latent TB infection, they possess TB bacteria in their body but it's inactive which means there are no such symptoms to be seen. Radiopharmaceuticals, with their ability to emit radiation and provide functional imaging, have emerged as valuable tools in TB management. This abstract presents an overview of the advancements and applications of radiopharmaceuticals in tuberculosis diagnosis and therapy.

Diagnostic radiopharmaceuticals, primarily based on gamma-emitting isotopes like Technetium-99m and Fluorine-18, have proven influential in visualizing active TB lesions within the lungs and extrapulmonary sites. Utilizing single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging modalities, these agents aid in precise lesion localization, enabling accurate disease staging and treatment planning. Furthermore, novel in vivo imaging agents have been developed to target specific molecular markers associated with TB infection, facilitating early detection and monitoring of treatment response. These targeted radiopharmaceuticals offer a promising approach to better understand the pathogenesis of TB and identify potential biomarkers for improved disease management. Radiopharmaceuticals have the potential to transform tuberculosis diagnosis and treatment, but there are still challenges to overcome, such as regulatory approvals, cost effective and accessibility in resource-limited areas.

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1.Introduction

It's true that tuberculosis, also known as TB, is a serious bacterial infection caused by *Mycobacterium tuberculosis*. It can affect the lungs and other parts of the body like brain, spine, and kidneys. (MayoClinic, n.d.) It is a major global health concern because it spreads through the air when an infected person coughs or sneezes. Despite medical advances, TB remains a significant public health issue, especially in developing countries where healthcare and resources are limited. The emergence of drug-resistant TB strains has made it even more difficult to control and eliminate the disease. (Bloom BR, 2017). Symptoms of TB include persistent coughing, chest pain, weakness, weight loss, fever, and night sweats. It can be latent, where the bacteria remain inactive in the body without causing symptoms, or active, where the infection becomes active, leading to illness. [3] (webmd.com, 2020). It is essential to diagnosis tuberculosis at early stage to prevent the spread of TB and start treatment as soon as possible to improve the chances of a successful recovery. Treatment usually involves a combination of antibiotics taken over a long period of time, typically six months or longer, to ensure complete eradication of the bacteria. Efforts to address tuberculosis on multiple fronts, including research and awareness campaigns, are essential to reduce its impact on individuals and communities.

Latest Drugs for Tuberculosis

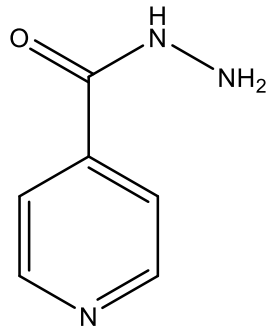
As of the last update in September 2021, the latest tuberculosis (TB) drug that was approved in India is Pretomanid. Pretomanid is an oral drug used in combination with other TB drugs for the treatment of extensively drug-resistant tuberculosis (XDR-TB) and treatment-intolerant or non-responsive multidrug-resistant tuberculosis (MDR-TB). (More, 2021).

First Line Anti-Tubercular Drugs

The first-line drugs for tuberculosis (TB) are a group of antibiotics that are considered the most effective and commonly used in the standard TB treatment regimen. These drugs have been widely studied and have shown good efficacy in treating TB infections. The first-line drugs are Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA), Ethambutol (EMB) and Streptomycin (SM). (Essouissi, 2012). The combination of these drugs is typically used for the treatment of active TB to maximize effectiveness and reduce the risk of developing drug-resistant strains. This combination therapy is known as Directly Observed Treatment Short-Course (DOTS) and is recommended by the World Health Organization (WHO) and other health authorities for TB

treatment. (Roohi, 2006). It's crucial to follow the prescribed treatment plan for TB and complete the full treatment course to prevent the recurrence of TB and drug-resistant TB strains.

ISONIAZID (Isonicotinic acid/ INH):



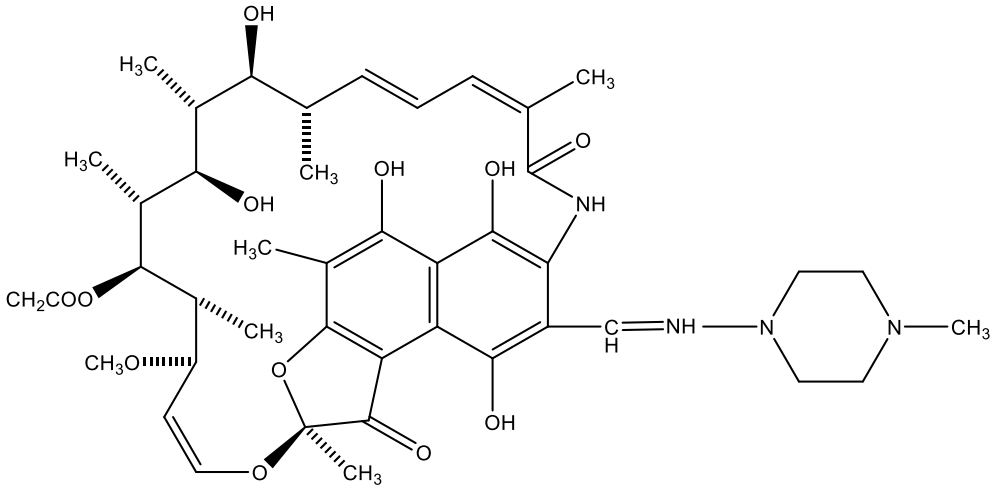
Isoniazid, commonly abbreviated as INH, is an essential medication used in the treatment of tuberculosis (TB) and other mycobacterial infections. (Samuel, 2005) It is one of the primary drugs in the standard TB treatment regimen, known as the first-line drugs. When used to treat active TB, isoniazid is typically administered in combination with other first-line drugs, such as rifampicin, pyrazinamide, and ethambutol, as part of a multi-drug treatment regimen. This combination therapy is crucial to prevent the development of drug-resistant strains and to increase the effectiveness of the treatment. (Chakraborty S, 2019).

MOA: The isoniazid when enters sensitive mycobacterial cell wall, it gets converted to an active form by KatG a mycobacterial catalase peroxidase enzyme. Then the activated isoniazid forms a covalent complex with InhA and KasA which are two crucial carrier proteins involved in the synthesis of mycolic acids. Mycolic acids are a component of mycobacterial cell wall. This results in inhibition of mycobacterial cell wall synthesis. Also, Isoniazid inhibits mycobacterial DHFrase (Dihydrofolate reductase) which results in the inhibition of bacterial DNA synthesis. (Vallabhajosula S, 2012)

Resistance: When mutations occur in KatG (catalase peroxidase enzyme) it inhibits the generation of active isoniazid. Mutations also occur in InhA gene due to over production of InhA protein. This can be overcome by increasing the dose of isoniazid. (Kulkarni M, 2012)

Adverse drug reaction: Neurotoxicity is due to interference in production of active coenzyme Pyridoxal. Pyridoxal is administered prophylactically to prevent neurotoxicity, Hepatitis, Fever, and skin rashes.

RIFAMPIN (rifampicin, R):



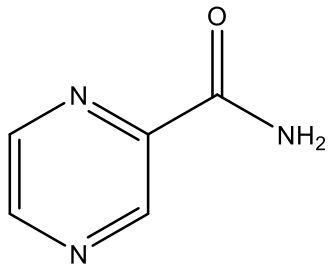
A semisynthetic derivative of rifamycin B obtained from *streptomyces mediterranei.* It's Bactericidal to *M. tuberculosis* active against many other gram-positive & gram-negative bacteria like *staph. Aureus, N. meningitidis, H.influenza, E coli, klebsiella, pseudomonas* etc. (Bitton KE, 2004). It is as efficient as INH and far better than all other drugs. It is also active against *M. leprae* which is highly sensitive. Both extracellular and intracellular bacilli are affected, therefore it has good sterilizing and resistance preventing actions. (Sathekge M, 2006)

MOA: When Rifampin binds to B-subunit of mycobacterial DNA-dependent RNA polymerase (encoded by rpoB gene) it blocks the polymerizing function of DNA-dependent RNA polymerase. This inhibits RNA synthesis. Rifampin also shows bactericidal action for both intracellular and extracellular mycobacteria. (Vallabhajosula S J. Y.-J., 2005)

RESISTANCE: mutation in rpoB gene reduced affinity for rifampin. (thekge M, 2016)

Adverse drug reaction: Hepatitis, Flushing, pruritis, rash, flu like symptoms, Abdominal cramps.

PYRAZINAMIDE (Z):



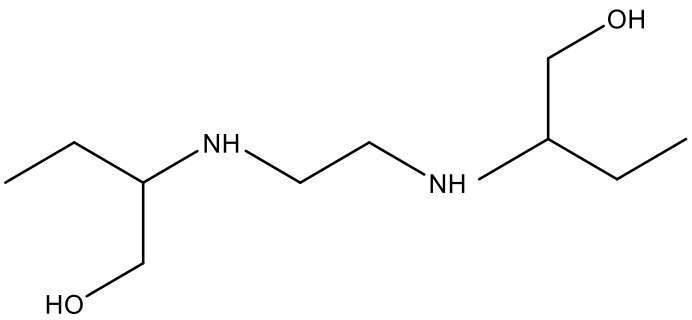
It is chemically like INH, it's a weaker tuberculocidal than INH and more active in acidic medium. It acts more lethal to intracellularly located bacilli. Used in anti-TB regimens to reduce the duration of treatment and to reduce the kill risk of relapse as it kills the residual intracellular bacilli. (Kaira K, 2008).

MOA: Pyrazinamide when enters the mycobacterial, it gets converted to pyranzinoic acid by the mycobacterial enzyme pyrazinamide (encoded by pncA gene). Pyrazinoic acid inhibits mycolic acid synthesis which disrupts mycobacterial cell membrane thus shows bactericidal action. (Sathekge M G.-P. F., 2019)

RESISTANCE: Due to mutation in pncA gene. (Bomanji J, 58(10))

Adverse drug reaction: Hepatotoxicity, Hyperuricemia and gout, Flushing, rashes, fever.

ETHAMBUTOL (E):



It is an antimycobacterial agent that is most used to treat tuberculosis as a combination with another drug. (Pandey U, 2019). It is employed with the triple regimen of RHZ *(rifampin + isoniazid + pyrazinamide)*

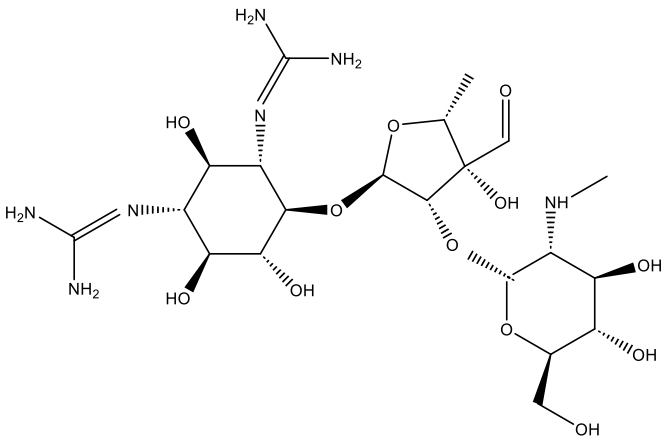
MOA: The embA gene, which encodes arabinosyl transferase. Arabinosyl transferase catalyzes the synthesis of arabinogalacton and facilitates the incorporation of mycolic acid in

mycobacterial cell wall. Ethambutol inhibits the enzyme arabinosyl transferase which inhibits the incorporation of mycolic acid to mycobacterial cell wall. (Sathekge M A. A., 2017).

Resistance: When mutation occurs in embB gene it leads to reduction in affinity of arabinosyl transferase for ethambutol. (Vallabhajosula S M. A., 1989).

Adverse drug reaction: Optic neuritis with blurred vision, visual disturbance & colour blindness.

SREPTOMYCIN (S):



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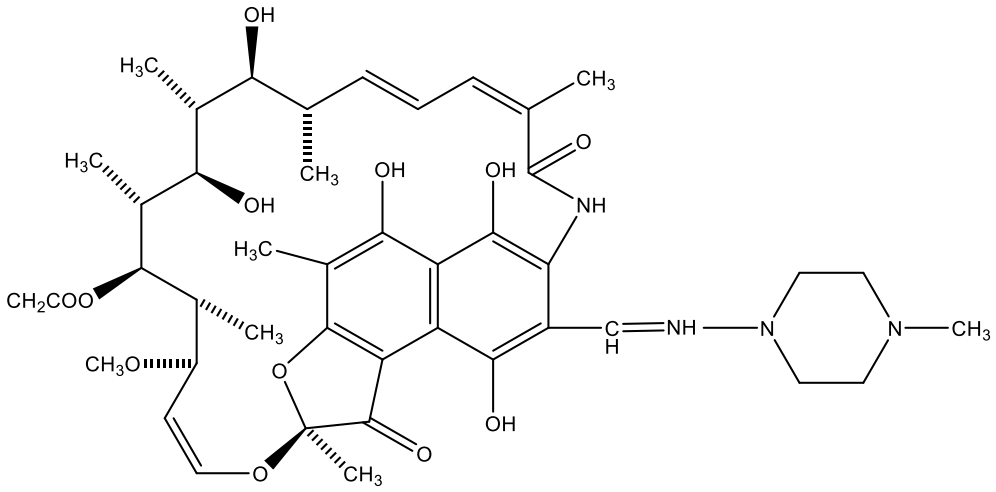

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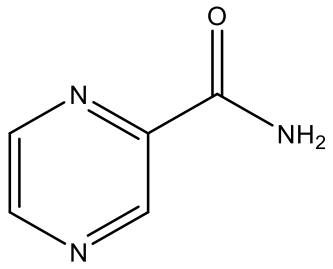

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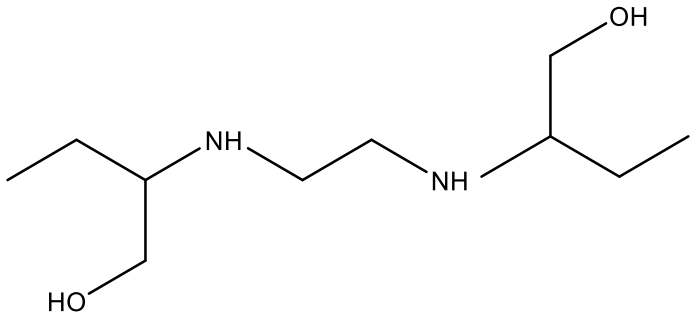

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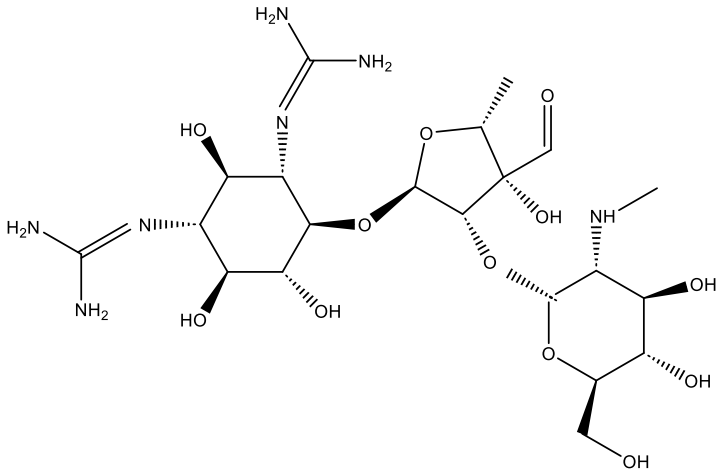


The first clinically used antitubercular drug and it's a tuberculocidal. It is less effective than INH and rifampin. Belongs to aminoglycoside antibiotic category. It has poor penetrability into cells therefore acts only on extracellular bacillus. It is administered by injection into vein or muscle. (Pandey MK, 2012)

MOA: It functions as a protein synthesis inhibitor. It binds to 30s subunit of mycobacterial ribosome irreversibly and interferes with the binding site of tRNA of the 30s subunit. Thus cause the misreading of codon and inhibits the protein synthesis and ultimately death of cell. (Sathekge MM, 2011).

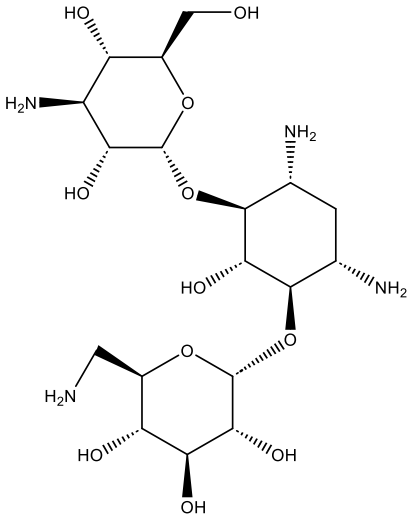
RESISTANCE: Because it is widely used alone the resistance developed rapidly, most patients had a relapse. Resistance had developed worldwide.

Adverse drug reaction: Ototoxicity & Nephrotoxicity.

Second Line Anti-Tubercular Drugs

These are those drug that are used for the treatment of drug resistant TB. These drugs cannot be taken without the supervision of an experienced doctor. These are less effective than first line drug and a less tolerated anti-TB drug used only in the cases of resistance to first line drug. (Pandey MK S. S., 2008)

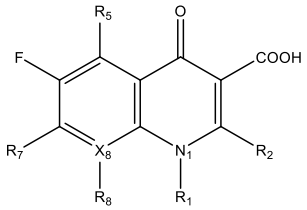
KANAMYCIN (Km), AMIKACIN (Am):



These are very similar to streptomycin and belong to the aminoglycoside antibiotics. Many streptomycin resistances are sensitive to this drug.

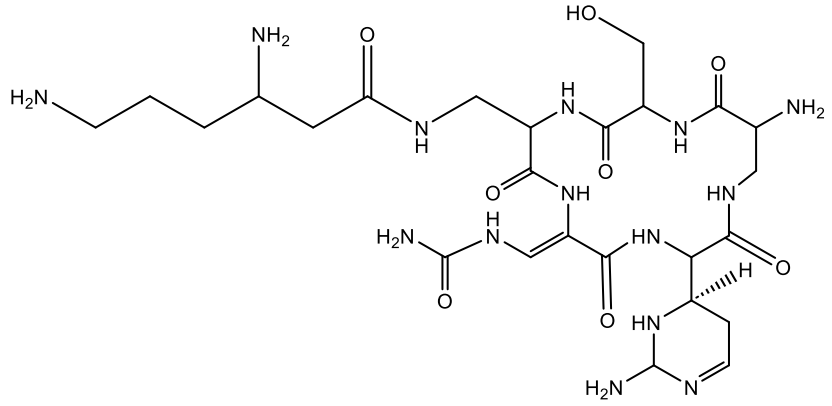
MOA: it works like that of streptomycin.

FLUROQUINOLONES(FQs):



These categories are highly effective antibiotics with many useful pharmacokinetic properties. (Bhalla M, 2014) drugs Like ofloxacin, levofloxacin, ciprofloxacin, moxifloxacin out of which moxifloxacin is the most active/potent oral bactericidal fluroquinolones against *M. tuberculosis* followed by levofloxacin, ofloxacin & ciprofloxacin.

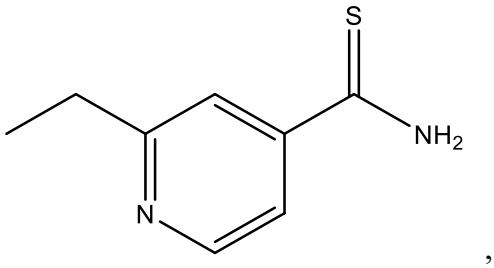
CAPREOMYCIN (Cm):



It's a cyclic peptide antibiotic which is very much different from aminoglycosides but has a similar mycobactericidal activity and is considered as a member of aminoglycoside. they have ability to kill wide variety of bacteria.

MOA: It is assumed to inhibit protein synthesis by binding to 70s ribosomal unit. Also bind with bacteria cell wall which results in abnormalities of protein. (Sathekge M A. A., 2018)

ETHIONAMIDE (Eto) & PROTHIONAMIDE (PTO):



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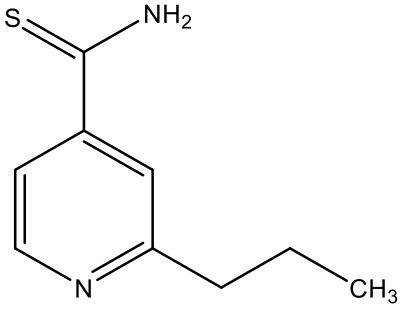

Both ethionamide and protionamide have efficacy and form crucial components of multi-drug resistance treatment regimen. (Vallabhajosula S S. I., 1989). It's an anti-tuberculocidal with moderate efficacy but acts on both intracellular and extracellular bacilli.

MOA: When ethionamide enters mycobacteria, it gets converted to active metabolites which further inhibits mycolic acid synthesis. (Sathekge M M. M., 2016)

2. Radiopharmaceuticals:

It is also known as *medicinal radiocompounds*. They are a group of pharmaceutical drugs containing radioactive isotopes. It can be used as a diagnostic and therapeutic medication for human diseases. Radiopharmaceuticals have the property to emit radiation themselves it has two constituents: a radionuclide and a pharmaceutical. Radiopharmaceuticals are used to diagnose problems but only small. (Pandey R, 2012). There are various types of radiopharmaceuticals, and they can be categorized based on their intended use and the radioactive element they contain.

Some common types of radiopharmaceuticals include:

1. Diagnostic Radiopharmaceuticals: These are used for imaging purposes to diagnose various medical conditions. They emit gamma rays, which are detected by imaging devices. Examples include Technetium-99m (Tc-99m), Iodine-131 (I-131), and Fluorine-18 (F-18). (Jha AK, 2013)

2. Therapeutic Radiopharmaceuticals: These are used to deliver targeted radiation to specific tissues or cancer cells for therapeutic purposes. They are employed in the treatment of certain cancers and other medical conditions. Examples include Iodine-131 for thyroid cancer and Strontium-89 for bone pain relief in patients with bone metastases. (Sathekge M A. A., 2017)

3. Radioimmunotherapeutics (RIT): RIT involves using radiolabeled monoclonal antibodies to target and destroy cancer cells. The radioactive element delivers radiation directly to cancer cells while sparing healthy tissues. (Pandey U M. A., 2014)

4. Positron Emission Tomography (PET) Tracers: PET radiopharmaceuticals contain positron-emitting isotopes and are used in PET scans to visualize metabolic and physiological processes in the body. Common PET tracers include Fluorine-18-fluorodeoxyglucose (F-18 FDG) used in oncology and Fluorine-18-florbetapir used for brain imaging in Alzheimer's disease. (Sathekge M A. A., 2015).

3. Ideal properties of radiopharmaceuticals

- It must have a short half-life isotope (the duration of ideally 1.5 times of the diagnostic procedure)
- The energy of Gamma rays: (100-250 keV)
- Must be a pure Gamma emitter.
- Target to non-target ratio.
- Localization in only desired tissue.
- Easy to prepare.

- Economically friendly. (Sathekge M M. A., 2011)

4. Examples of Radiopharmaceuticals:

Technetium-99M: It's a radioactive isotope of element technetium, it has a unique property for its wide use in nuclear medicine imaging. Tc-99m emits gamma rays which are detected by specialized camera to create little images of various organs and tissue. This isotope has a particular value in medical imaging because of its short half-life which is approx. 6hours. (Solanki KK, 1992). This allows for timely imaging procedure without prolonged radiation exposure to the patient.

MOA: Radioactive isotopes of techtenium-99m work by emitting gamma rays, which are detected using a gamma camera during medical imaging. These radiotracers are not confined to a specific organ and distribute evenly across various tissues. Once distributed, they emit photons that are captured and used for imaging through SPECT or PET scans. (Sathekge MM M. K., 2019).

Administration: Technetium radiotracer may be introduced into the body via injection, either intravenously or intramuscularly or orally. (Pandey R K. G., 2005)

IODINE-131: It's a radioactive isotope of iodine which has a half-life of about 8 days. It is specifically produced in nuclear reactors and during the detonation of nuclear weapons. It has a capability to emit high-energy beta particles and gamma rays due to its short half-life though it makes it more hazardous to human health if it is not handled properly. Iodine-131 is also helpful in medicine for diagnostic and therapeutic purposes, especially in treating thyroid disorder and certain types of cancer. (Sathekge M M. N., 2012)

MOA: The mechanism of action in medicinal applications particularly involves its radioactive properties targeting the thyroid gland. Iodine is taken up by the thyroid gland, once inside the thyroid gland it emits high-energy beta particles which further destroy nearby thyroid tissue. (Vallabhajosula S G. S., 2005)

FLUORINE-18: It is commonly denoted as F-18, is a radioactive isotope of fluorine and most repeatedly used radioisotopes in PET. which has a half-life of about 110 min. used in position emission tomography imaging to detect and visualize various metabolic activity in body. These

gamma rays are detected by PET scanners. Its radioactivity comes from an excess of protons and neutrons, making it unstable and prone to decay. (Sathekge M M. A., 2011)

MOA: The mechanism lies in its radioactive properties. F-18 undergoes decay by emitting a positron a positively charged particle. They incorporate into some specific molecules, once inside the body the radiotracer undergoes decay, emitting positron this positron travels a very short distance in tissue prior to encounter with electron. (Pandey R K. G., Antituberculous solid lipid nanoparticles as drug delivery vehicles: Use of nebulization for dry powder inhalation. , 2004)

5. Applications of Radiopharmaceuticals in diagnosis and management of Tuberculosis:

Radiopharmaceuticals have a limited significance in diagnosing and managing tuberculosis (TB). The primary diagnostic tool for TB is still the tuberculin skin test (TST) or the interferon-gamma release assay (IGRA), as they identify the immune response to mycobacterium tuberculosis bacteria. (Pandey R S. A., 2003). Radiopharmaceuticals have useful applications in diagnosing and evaluating tuberculosis-related complications. For instance, nuclear medicine imaging methods like SPECT or PET can be employed to detect active TB in the lungs or other body areas. (thekge M M. A., 2015) By using radiolabeled molecules such as leukocytes or antibodies, it is possible to target specific infection sites and effectively identify active tuberculosis. (Mukherjee A, 2015) Furthermore, radiopharmaceuticals have utility in research environments for exploring the disease mechanisms of tuberculosis and examining its interactions with the human body. Such studies can yield valuable knowledge about TB pathogenesis and potential strategies for treatment.

It's essential to highlight that radiopharmaceuticals are not the primary method for diagnosing TB. Traditional diagnostic methods, along with appropriate medical evaluation and laboratory tests, remain the standard for identifying and managing tuberculosis cases. (Pandey R K. G., Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis., 2005). There are several types of TB with several different types of tests, yet the diagnosis of extra-pulmonary TB has been more difficult, and method being used are either inaccurate or very painful and require offensive sample taking from the bone which might lead to the infection especially in rural area. (Sathekge M M. A., 2015) It’s a new technique developed which is believed to be more reliable and less painful to the patient.

6. Conclusion:

In conclusion, radiopharmaceuticals offer a comprehensive approach to combat tuberculosis. It can be used to both diagnosis and treatment of tuberculosis. They can help doctors better visualize the disease and develop more precise treatment strategies. It's important for researchers, clinicians, and policymakers to work together to fully harness the potential of these tools in the fight against tuberculosis.

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