IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
May 2015 Vol.:1, Issue:1

An Overview on Pharmacokinetic Profile of Drugs Used in the Treatment of TB with HIV Co-infection

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

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Submission: 17 April 2015
Accepted: 30 April 2015
Published: 10 May 2015

Keywords: tuberculosis, HIV, co-infection, Pharmacokinetic Profile

ABSTRACT

The World Health Organization estimates that of the 8.7 million individuals who developed incident tuberculosis in 2011, 1.1 million, or 13%, were co-infected with HIV. Further, of those who suffer tuberculosis-related mortality, 31% are HIV-infected. Despite the complexities of simultaneously treating two infections requiring multidrug therapy, antiretroviral therapy is life-saving among patients with tuberculosis and advanced HIV disease. Isoniazid is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme that in *Mycobacterium tuberculosis* is called KatG. Ethambutol is used along with other medications to treat a number of infections, including tuberculosis, *Mycobacterium avium complex*, and *Mycobacterium kansasii*.

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INTRODUCTION

Worldwide, tuberculosis is the most common serious opportunistic infection among people with HIV infection. The World Health Organization estimates that of the 8.7 million individuals who developed incident tuberculosis in 2011, 1.1 million, or 13%, were co-infected with HIV. Further, of those who suffer tuberculosis-related mortality, 31% are HIV-infected. Despite the complexities of simultaneously treating two infections requiring multidrug therapy, antiretroviral therapy is life-saving among patients with tuberculosis and advanced HIV disease (1).

India is estimated to have around 1.16 lakhs annual new HIV infections among adults and around 14,500 new HIV infections among children in 2011. Of the 1.16 lakhs, estimated new infections in 2011 are among adults. The six high prevalence states account for only 31% of new infections, while the ten low prevalence states of Odisa, Jharkhand, Bihar, Uttar Pradesh, West Bengal, Gujarat, Chhattisgarh, Rajasthan, Punjab & Uttarakhand together account for 57% of new infections. The greater vulnerabilities in these states are being given higher focus in the AIDS control programme.

The total number of PLHIV in India is estimated at 21 lakhs in 2011. Children (<15 yrs) account for 7% (1.45 lakhs) of all infections, while 86% are in the age group of 15-49 years. Of all HIV infections, 39% (8.16 lakhs) are women. The estimated number of PLHIV in India maintains a steady declining trend from 23.2 lakhs in 2006 to 21 lakhs in 2011. From a programmatic point of view, screening of all HIV-infected persons for tuberculosis and vice-versa will help identify co-infected patients who require treatment for both infections. This requires good coordination and communication between the TB and AIDS control programs, in India varied widely and ranged from 1% to 13.8% across the 15 districts (Central TB Division, unpublished observations).

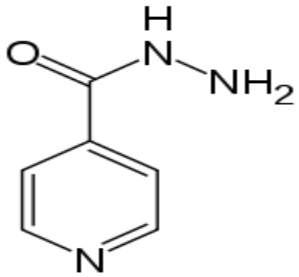
Prevalence states of South India (Andhra Pradesh, Karnataka, Maharashtra, and Tamil Nadu) account for 53% of all HIV infected population in the country (2).

DRUGS USED IN TREATMENT OF TUBERCULOSIS WITH AIDS CO-INFECTION:

1. ISONIAZID

Isoniazid (also known as isonicotinylhydrazine (or INH), is an organic compound that is the first-line medication in prevention and treatment of tuberculosis. The compound was first synthesized in the early 20th century, but its activity against tuberculosis was first reported in the early 1950s.

STRUCTURE



PHARMACOLOGY	
Protein binding	Very low (0-10%)
Metabolism	liver; CYP450: 2C19, 3A4 inhibitor
Half-life	0.5-1.6h (fast acetylators), 2-5h (slow acetylators)
Excretion	urine (primarily), feces

Mechanism of Action

Isoniazid is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme that in *Mycobacterium tuberculosis* is called KatG. KatG couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthase. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall. A range of radicals are produced by KatG activation of isoniazid, including nitric oxide, which has also been shown to be important in the action of another antimycobacterial prodrug PA-824.

Isoniazid is bactericidal to rapidly dividing mycobacteria, but is bacteriostatic if mycobacteria are slow-growing. It induces the P450 system and hence acts as a source of free radicals.

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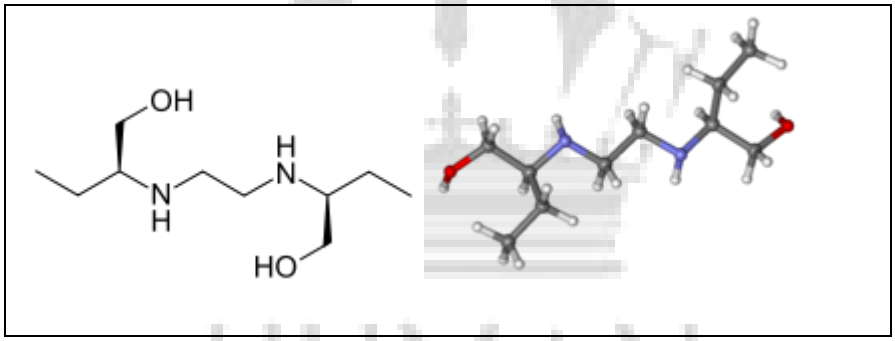
Isoniazid is widely distributed to all fluids and tissues, including CSF, pleural and ascitic fluids, skin, sputum, saliva, lungs, and muscle. It crosses the placenta and is distributed into breast milk.

2. ETHAMBUTOL

Ethambutol (commonly abbreviated EMB or simply E) is a bacteriostatic, antimycobacterial drug prescribed to other tuberculosis drugs, such as isoniazid, rifampicin and pyrazinamide. Ethambutol is used along with other medications to treat a number of infections, including tuberculosis, *Mycobacterium avium complex*, and *Mycobacterium kansasii*.

STRUCTURE



PHARMACOLOGY	
Routes of administration	Oral
Metabolism	Hepatic
Elimination half-life	3–4 hours
Protein binding	20–30%
Excretion	Renal

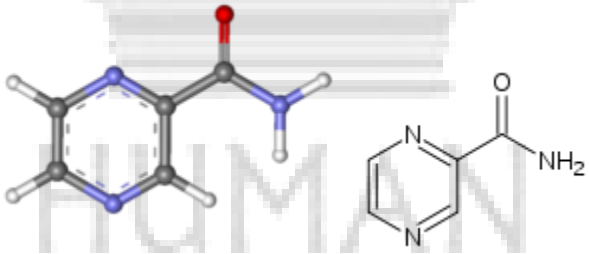
Mechanism of action

Ethambutol is bacteriostatic against actively growing TB bacilli. It works by obstructing the formation of cell wall. Mycolic acids attach to the 5' arabinogalactan-peptidoglycan complex in the cell wall. It disrupts arabinogalactan synthesis by inhibiting the enzyme arabinosyl transferase. Disruption of the arabinogalactan synthesis inhibits the formation of this complex and leads to increased permeability of the cell wall (2).

3. PYRAZINAMIDE

Pyrazinamide is a prodrug that stops the growth of *Mycobacterium tuberculosis*. Pyrazinamide diffuses into *M. tuberculosis*, where the enzyme pyrazinamidase converts pyrazinamide to the active form pyrazinoic acid. Under acidic conditions, the pyrazinoic acid that slowly leaks out converts to the protonated conjugate acid, which is thought to diffuse easily back into the bacilli and accumulate. The net effect is that more pyrazinoic acid accumulates inside the bacillus at acid pH than at neutral pH.

STRUCTURE



PHARMACOLOGY	
Bioavailability	>90%
Metabolism	Hepatic
Half-life	9 to 10 hours
Excretion	Renal

Mechanism of action

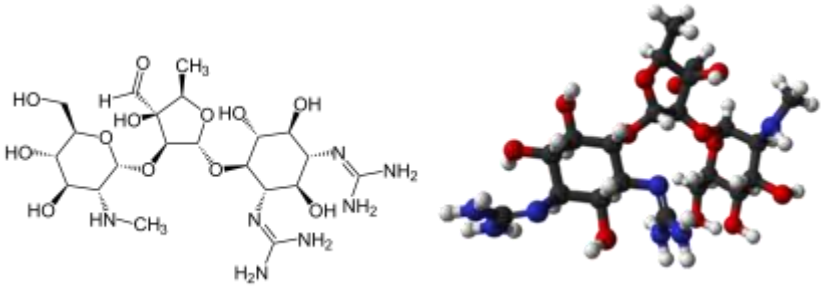
Pyrazinoic acid was thought to inhibit the enzyme fatty acid synthase (FAS) I, which is required by the bacterium to synthesize fatty acids although this has been discounted. It was also suggested that the accumulation of pyrazinoic acid disrupts membrane potential and interferes with energy production, necessary for survival of M. tuberculosis at an acidic site of infection. Further studies reproduced the results of FAS I inhibition as the putative mechanism first in whole cell assay of replicating *M. tuberculosis* bacilli which have shown that pyrazinoic acid and its ester inhibit the synthesis of fatty acids. This study was followed by *in vitro* assay of tuberculous FAS I enzyme that tested the activity with pyrazinamide, pyrazinoic acid and several classes of pyrazinamide analogs. Pyrazinamide and its analogs inhibited the activity of purified FAS I. Pyrazinoic acid binds to the ribosomal protein S1 (RpsA) and inhibits trans-translation. This may explain the ability of the drug to kill dormant mycobacteria.

Mutations in the *pncA* gene, which encodes a pyrazinamidase, is responsible for the appearance of most pyrazinamide resistant *M. tuberculosis* strains. A few pyrazinamidase resistant strains with mutations in the *rpsA* gene have also been identified (3).

4. STREPTOMYCIN

Streptomycin is an antibiotic (antimycobacterial) drug, the first of a class of drugs called aminoglycosides to be discovered, and it was the first effective treatment for tuberculosis. It is derived from the actinobacterium *Streptomyces griseus*. Streptomycin is a bactericidal antibiotic. Adverse effects of this medicine areototoxicity, nephrotoxicity, fetal auditory toxicity, and neuromuscular paralysis**.**

STRUCTURE



PHARMACOLOGY	
Bioavailability	84% to 88% (est.)
Half-life	5 to 6 hours
Excretion	Renal

Mechanism of action

Streptomycin is a protein synthesis inhibitor. It binds to the small 16S rRNA of the 30S subunit of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit. This leads to codon misreading, eventual inhibition of protein synthesis and ultimately death of microbial cells through mechanisms that are still not understood. Speculation on this mechanism indicates that the binding of the molecule to the 30S subunit interferes with 50S subunit association with the mRNA strand. This results in an unstable ribosomal-mRNA complex, leading to a frameshift mutation and defective protein synthesis; leading to cell death. Humans have ribosomes which are structurally different from those in bacteria, so the drug does not have this effect in human cells. At low concentrations, however, streptomycin only inhibits growth of the bacteria by inducing prokaryotic ribosomes to misread mRNA. Streptomycin is an antibiotic that inhibits both Gram-positive and Gram-negative bacteria, and is therefore an useful broad-spectrum antibiotic (4).

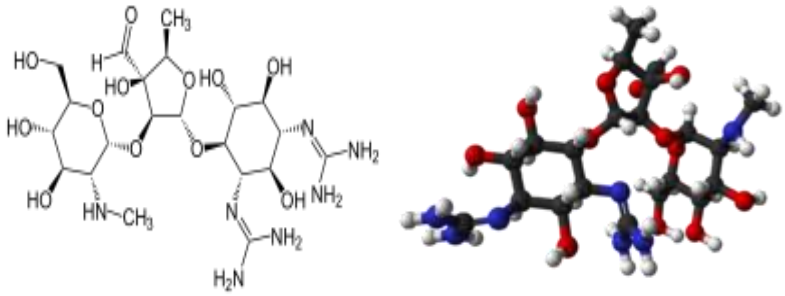
5. RIFAMPICIN

Rifampicin (INN, BAN) or rifampin (USAN) is a bactericidal antibiotic drug of rifamycin group.

Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase. Rifampicin may be abbreviated R, RMP, RA, RF, or RIF (US).

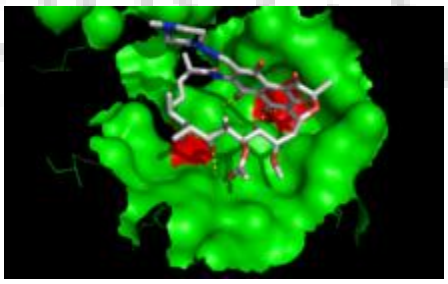
Rifampicin is also known as rifaldazine, RMP, rofact (in Canada), and rifampin in the United States. There are various types of rifamycins from which this is derived, but the rifampicin form, with a 4-methyl-1-piperazinaminyl group, is by far the most clinically effective. Rifampicin can also be derived from rifamycin S.

STRUCTURE



PHARMACOLOGY	
Bioavailability	90 to 95% oral
Protein binding	80%
Metabolism	Hepatic and intestinal wall
Half-life	3-4 hours

Mechanism of action



Binding of rifampicin in the active site of RNA polymerase. Mutation of amino acids shown in red are involved in resistance to the antibiotic.

Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase.

Crystal structure data and biochemical data indicate that rifampicin binds to RNA polymerase at a site adjacent to the RNA polymerase active center and blocks RNA synthesis by physically blocking the formation of the phosphodiester bond in the RNA backbone, preventing extension of RNA products beyond a length of 2-3 nucleotides ("steric-occlusion" mechanism).

Resistance to rifampicin arises from mutations that alter residues of the rifampicin binding site on RNA polymerase, resulting in decreased affinity for rifampicin. Resistant mutations map to the *rpoB* gene, encoding RNA polymerase beta subunit (5).

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