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"A Review Article An Isoniazid"

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Abstract
Isoniazid, a cornerstone drug in the treatment of tuberculosis (TB), has been a mainstay in global TB control efforts since its introduction in the 1950s. It is a first-line agent used in both active and latent TB infections, valued for its high efficacy, affordability, and ease of administration. Isoniazid is a prodrug that targets Mycobacterium tuberculosis by inhibiting mycolic acid synthesis, a critical component of the bacterial cell wall, leading to bacterial death. Its pharmacokinetic profile includes rapid absorption, wide distribution, and metabolism influenced by genetic polymorphisms of the N-acetyltransferase 2 (NAT2) enzyme, which classifies individuals as slow or fast acetylators. This genetic variability impacts drug efficacy and toxicity, particularly hepatotoxicity and peripheral neuropathy, which are the most significant adverse effects associated with Isoniazid. These can be mitigated by close monitoring and pyridoxine (Vitamin B6) supplementation. Despite its indispensable role, the emergence of drug-resistant strains, such as multidrug-resistant TB (MDR-TB), and adverse effects pose significant challenges to its utility. Research is focused on overcoming these limitations through innovations in drug delivery systems, such as nanoformulations, and combination therapies aimed at reducing resistance and toxicity. Isoniazid's enduring importance in TB treatment highlights its pivotal role in public health. Continued research and advancements in pharmacology are essential to maintain its efficacy and address the challenges of drug resistance and adverse effects. This review provides a comprehensive overview of Isoniazid's pharmacology, therapeutic applications, challenges, and future directions in TB management.
Key Words: *Isoniazid, Tuberculosis, Pharmacokinetic, Bacteriostatic, Toxicity, Bioavailability, Etc.*

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I. Literature Of Review

• **Goodman & Gilman (2021) –** The Pharmacological Basis of Therapeutics, 13th Edition. Authors: Laurence L. Brunton, Randa Hilal-Dandan, and Bjorn C. Knollmann.
Publisher: McGraw-Hill Education.

• **Katzung, B. G., Trevor, A. J. (2021) –** Basic & Clinical Pharmacology, 15th Edition.
Publisher: McGraw-Hill Education.

• **British National Formulary (BNF) (2024) –** BNF 86.
Publisher: BMJ Group and Pharmaceutical Press.

II. Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is one of the most significant infectious diseases globally, particularly in low- and middle-income countries. Despite advancements in healthcare, TB continues to pose a substantial burden due to its high morbidity and mortality rates. Effective pharmacological interventions are critical to controlling the disease, and Isoniazid has been a cornerstone of TB treatment since its discovery in the 1950s. Isoniazid, a first-line anti-TB drug, is a key component of the World Health Organization (WHO)-recommended multi-drug therapy. Its primary role lies in its ability to effectively target actively dividing M. tuberculosis, making it bactericidal in nature. Additionally, its utility extends to treating latent TB infections (LTBI), thereby preventing the progression to active disease in individuals at high risk, such as immunocompromised patients. Administered as part of combination regimens, Isoniazid minimizes the risk of resistance development when used alongside drugs like Rifampin and Pyrazinamide. Its simple oral dosing, cost-effectiveness, and broad availability make it indispensable in both public health and clinical settings. The emergence of drug-resistant strains and concerns about adverse effects, including hepatotoxicity and peripheral neuropathy, present ongoing challenges. These factors necessitate vigilant monitoring and the exploration of adjunct therapies to sustain its effectiveness. This review delves into the pharmacology, mechanism of action, clinical applications, and challenges associated with Isoniazid, highlighting its vital role in combating TB while addressing future directions for optimizing its use.

III. Structure Of Isoniazid

Isoniazid, chemically known as isonicotinylhydrazide, is a simple organic compound with the molecular formula **C6H7N3O** and a molecular weight of 137.14 g/mol. Its structure consists of two main functional groups[21]

- **Pyridine Ring**: A six-membered aromatic ring containing one nitrogen atom, forming the core structure.
- **Hydrazide Group (-CONHNH2)**: Attached to the pyridine ring at the meta position (3rd carbon), this group is essential for the drug's activity.

Key Structural Features

- **Prodrug Nature**: Isoniazid's hydrazide group is critical for its activation within Mycobacterium tuberculosis by the enzyme catalase-peroxidase (KatG).
- **Small Molecular Size**: Enables efficient diffusion into bacterial cells and across biological membranes, including penetration into the central nervous system (CNS), making it effective for TB meningitis.[1]
- **Hydrophilic Nature**: The presence of polar groups (hydrazide and pyridine nitrogen) makes Isoniazid water-soluble, aiding in oral administration and rapid absorption.

Chemical Representation

- **IUPAC Name**: Pyridine-4-carbohydrazide
- **Structural Formula**:

O||C-NH-NH2|C6H4-N

Implications Of Its Structure

The simplicity and reactivity of Isoniazid's structure contribute to its activation mechanism within the bacterial cell. Once activated, the hydrazide group facilitates the formation of reactive intermediates that inhibit mycolic acid synthesis, which is critical for the integrity of the bacterial cell wall.[2]

IV. Mechanism Of Action Of Isoniazid

Isoniazid is a prodrug that requires enzymatic activation within Mycobacterium tuberculosis to exert its bactericidal effects. Its mechanism of action primarily targets the synthesis of mycolic acids, which are essential components of the mycobacterial cell wall.[3]

Activation

Isoniazid is activated by the bacterial enzyme **catalase-peroxidase** (encoded by the katG gene). Upon activation, Isoniazid forms reactive intermediates, including the isonicotinic acyl-NAD adduct.

Inhibition Of Mycolic Acid Synthesis

The activated form of Isoniazid binds to and inhibits **InhA** (enoyl-acyl carrier protein reductase), an enzyme critical for the biosynthesis of mycolic acids.

- **Mycolic Acids**: Long-chain fatty acids that are unique to the cell walls of mycobacteria, providing structural integrity and resistance to environmental stress and antibiotics.
- Inhibition of InhA disrupts mycolic acid synthesis, leading to a weakened cell wall and eventual bacterial lysis.

Selective Toxicity

Isoniazid's action is highly specific to M. tuberculosis because the activation enzyme KatG and the target enzyme InhA are unique to mycobacteria.[19]

Bactericidal And Bacteriostatic Effects

- **Bactericidal**: Against actively dividing mycobacteria, as it disrupts cell wall synthesis.
- **Bacteriostatic**: Against dormant mycobacteria, where metabolic activity is reduced, limiting mycolic acid synthesis.

Resistance Mechanisms

Resistance to Isoniazid typically arises from mutations in the:

- **katG gene**: Reduces activation of the drug.
- **inhA promoter region**: Increases the expression of the target enzyme, reducing drug binding.

V. Clinical Pharmacology Of Isoniazid

Isoniazid is a first-line anti-tuberculosis agent that has been extensively used in the treatment and prevention of Mycobacterium tuberculosis infections. Its clinical pharmacology includes pharmacokinetics, pharmacodynamics, therapeutic applications, and safety profile. These factors together define its effectiveness and limitations in tuberculosis management.[17]

Pharmacokinetics

Absorption

- Isoniazid is well-absorbed from the gastrointestinal tract after oral administration, with bioavailability approaching 100%.[23]
- Peak plasma concentrations are typically achieved within 1–2 hours post-administration.[11]
- Food can delay absorption and reduce peak plasma levels, so it is often recommended to take the drug on an empty stomach.

Distribution

- Isoniazid is widely distributed throughout the body, including the lungs, liver, and cerebrospinal fluid (CSF).
- It penetrates well into caseous lesions and the central nervous system, making it effective in treating tuberculosis meningitis.
- The drug also crosses the placenta and is excreted in breast milk.

Metabolism

- Isoniazid is primarily metabolized in the liver by **N-acetyltransferase 2 (NAT2)** via acetylation.
- Genetic polymorphisms in NAT2 result in two distinct groups:
  - **Slow acetylators**: Higher plasma levels, prolonged half-life, and increased risk of toxicity.
  - **Fast acetylators**: Lower plasma levels and reduced therapeutic efficacy.
- The major metabolite is **acetylisoniazid**, which is further hydrolyzed to inactive compounds.[21]

Excretion

- Isoniazid and its metabolites are primarily excreted in the urine, with a small fraction eliminated through feces and sweat.
- The elimination half-life ranges from 0.5 to 3 hours, depending on the acetylation phenotype.[16]

Pharmacodynamics

- **Mechanism of Action**: Isoniazid targets mycolic acid synthesis by inhibiting the bacterial enzyme **InhA**, essential for mycobacterial cell wall formation.
- **Bactericidal Activity**: Effective against actively dividing bacilli.
- **Bacteriostatic Activity**: Against dormant bacilli with low metabolic activity.
- The drug demonstrates **time-dependent killing**, necessitating sustained exposure for optimal effect.[5]

Therapeutic Applications

Treatment Of Active Tuberculosis

- Isoniazid is a critical component of the standard **HRZE regimen** (Isoniazid, Rifampin, Pyrazinamide, Ethambutol) for drug-susceptible TB.
- It is administered daily or intermittently (thrice-weekly) for the initial two months, followed by continuation with Isoniazid and Rifampin for four months.[11]

Latent Tuberculosis Infection (Ltbi)

- Isoniazid monotherapy for 6–9 months is highly effective in preventing the progression of LTBI to active TB.
- Alternative shorter regimens include Isoniazid plus Rifapentine (3 months) or Isoniazid plus Rifampin (4 months).

Tuberculosis Meningitis And Extrapulmonary Tuberculosis

- Due to its excellent CSF penetration, Isoniazid is effective in treating TB meningitis and other forms of extrapulmonary TB.[3]

Adverse Effects

Hepatotoxicity

- The most common and serious side effect, ranging from mild transaminitis to acute hepatic failure.

- Risk factors: Older age, alcohol use, pre-existing liver disease, and slow acetylation phenotype.
- Monitoring of liver enzymes is essential during therapy.

Peripheral Neuropathy
- Results from pyridoxine (Vitamin B6) deficiency caused by Isoniazid.
- Preventable by co-administration of pyridoxine (10–50 mg/day).
- Particularly common in malnourished individuals, diabetics, and pregnant women.

Hypersensitivity Reactions
- Includes rash, fever, and, rarely, systemic symptoms like drug-induced lupus.

Neurological Effects
- High doses can cause seizures, psychosis, or encephalopathy due to inhibition of gamma-aminobutyric acid (GABA) synthesis.

Gastrointestinal Effects
- Nausea, vomiting, and epigastric discomfort may occur in some patients.

Drug Interactions
- Isoniazid inhibits hepatic cytochrome P450 enzymes, potentially increasing plasma levels of drugs such as:
  - Phenytoin
  - Carbamazepine
  - Warfarin
  - Benzodiazepines
- Rifampin co-administration can induce hepatic enzymes, accelerating Isoniazid metabolism and reducing its levels.

Special Populations
Pregnant And Breastfeeding Women
- Isoniazid is considered safe during pregnancy but requires pyridoxine supplementation to prevent neuropathy.
- It is excreted in breast milk but does not pose significant risks to breastfeeding infants.[13]

Patients With Liver Disease
- Use with caution in patients with liver impairment; dose adjustments may be required.

Resistance
- Resistance to Isoniazid is primarily due to mutations in the **katG** gene (impairs drug activation) or the **inhA** promoter region (reduces drug binding).[8]
- Resistance is a defining feature of multidrug-resistant TB (MDR-TB), requiring second-line drugs for management.

VI. UV Spectroscopy And Concentration Determination Of Isoniazid

Isoniazid (INH) is a first-line anti-tubercular drug, commonly analyzed using UV spectroscopy for quantification. Its absorbance in the UV range is measured to determine its concentration, adhering to **Beer-Lambert's law**.

Key Details For Uv Spectroscopy Of Isoniazid
- **Maximum Wavelength (λmax\lambda_{\text{max}}λmax)**
  - Isoniazid shows maximum absorbance in the range of **260–280 nm**. The exact wavelength depends on the solvent and pH of the medium.[2]
  - **Solvent:**
  - Commonly used solvents:
    - **Distilled water**
    - **Phosphate buffer (pH 6.8 or 7.4)**

- **Concentration Range**
  - Isoniazid solutions are typically linear in the concentration range of **10–50 µg/mL** for UV analysis.
- **Calibration Curve**

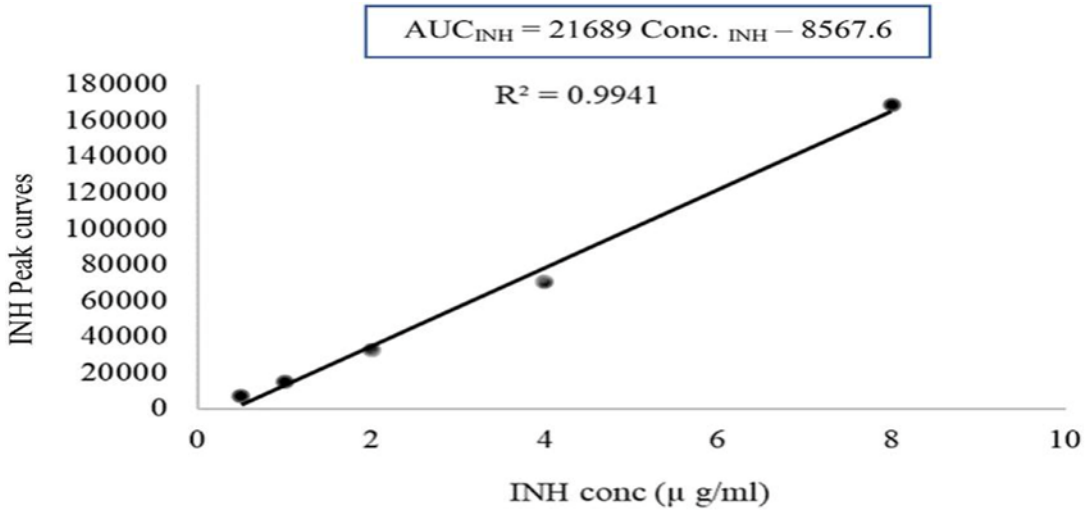

Figure. 1.Calibration Curve Of Isoniazid

- A calibration curve is created by measuring the absorbance of standard solutions at λmax\lambda_{\text{max}}λmax and plotting concentration (x-axis) vs. absorbance (y-axis).
- The linear regression equation y=mx+cy = mx + cy=mx+c is used to relate absorbance to concentration.[Including Articles]

VII. Steps For Quantification

1. **Preparation of Stock Solution:**
   - Dissolve a known quantity of isoniazid (e.g., 10 mg) in 100 mL of distilled water or buffer to prepare a 100 µg/mL stock solution.
2. **Dilution:**
   - Dilute the stock solution to obtain working standards (e.g., 10, 20, 30, 40, and 50 µg/mL).
3. **Measurement:**
   - Measure the absorbance of each standard at λmax\lambda_{\text{max}}λmax using a UV-visible spectrophotometer.
4. **Unknown Sample:**
   - Measure the absorbance of the unknown sample and interpolate its concentration from the calibration curve.

VIII. Conclusion

The results of our analysis suggest that INH prophylaxis reduces the risk of TB by 59% among children ≤ 15 years of age, excluding a subset of young children on whom INH was initiated at four months of age or earlier for primary prophylaxis (RR = 0.41, 95% CI 0.31, 0.55 p < 0.001). INH confers a protective effect against TB among HIV negative children; however, we had insufficient data to make a definitive conclusion on efficacy of INH in preventing TB among HIV-infected children. In contrast to the WHO recommendation to give all HIV- infected children over 12 months of age isoniazid preventive therapy, our results show no effect of isoniazid preventive therapy among this group (though from limited data) and justifies more investigation. The results further suggest that INH is not effective among the youngest children and that there is little evidence of a mortality benefit in children of any age. Based on our results, we recommend the administration of INH to children at risk, especially those with smear positive contacts, because, as the evidence indicates, INH will reduce their risk of developing TB and thus help lower TB disease burden and TB-related years lost to disability (YLD).Due to the fact that there are limited data on the efficacy of INH in children ≤ five years of age, in HIV-infected children, and on overall mortality, we recommend that further studies be carried out to answer conclusively the question of whether INH is effective among very young children and children who are HIV-infected, as well as to determine the optimum duration of INH preventive therapy and to assess the mortality benefit among children.[EVALUATION DATA]

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