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TUBERCULOSIS CURE BY ISONIAZID: THE REVIEW PAPER

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ABSTRACT

Isoniazid is the most important heterocyclic moiety in organic and medicinal chemistry due to the existence of a reactive site in the molecule, which allows for its application in a variety of sectors. Isoniazid is the most important firstline medication for tuberculosis. Isoniazid's unique molecular structure makes it an ideal candidate for drug creation. Antitubercular medicines are currently used, however they can be hazardous and require prolonged treatment. Researchers have developed novel med ications and mimics of existing treatments for tuberculosis. Newer analogues with substantial antitubercular action and few side effects have been developed. They are effective against multidrug resistant mycobacterium and can also be used in patients with HIV/AIDS.

KEYWORDS: Tuberculosis, Isoniazid, Hepatotoxicity, Resistance, Mycolic acid.

INTRODUCTION

Because the molecule contains a reactive site that expands its use in a variety of applications, isoniazid is the most significant heterocyclic moiety in organic and medicinal chemistry. The most significant first-line medication for tuberculosis treatment is isoniazid.[1]

Anti-TB drug treatment started in 1944, when Streptomycin and paraaminosalicylic acid were Discovered. In 1950, the first trial was performed Comparing the efficacy of streptomycin and Paraaminosalicylic acid both as monotherapy or Combined. The study demonstrated that combined Therapy was more effective and resulted in the First multidrug anti-TB treatment that consisted of A long course of both drugs. In 1952, a third drug, Isoniazid, was added to the previous combination, Greatly improving the efficacy of treatment, but Which still had to be administered for 18-24 Months.[2] In 1960, ethambutol substituted Paraaminosalicylic acid, and the treatment course Was reduced to 18 months. In the'70s, with the Introduction of rifampicin

into the combination, Treatment was shortened to just nine months. Finally, in 1980, pyrazinamide was introduced Into the anti-TB treatment, which could be Reduced further to only six months.[3] Two Biological features explain why combined drug Therapy is more effective at curing TB than Monotherapy. One is that treatment of active TB With a single drug results in the selection of drug Resistant bacilli and failure to eliminate the Disease.[4] The other is that different populations of Tubercle bacilli-each of them showing a distinct Pattern of susceptibility for anti-TB drugs may Co- exist in a TB patient. Soon after the Introduction of the first anti-TB drugs, drug Resistant bacilli started to emerge, but the launch Of both combination therapy and new and more Effective drugs seemed to be enough to control The disease. In fact, it was thought that TB could Be eradicated by the end of 20th century.[5] However, TB unexpectedly re-emerged in the'80s, and in the following years there was an Important increase in the incidence of multiple-, And extensively drug resistant strains. Since 1970, No new drug has been discovered for anti-TB Treatment, which today seems insufficient to Confront the disease. Fortunately, research efforts Have been accomplished and today there is a wide Range of new molecules with promising anti-TB Activity.[6] According to data from the World Health Organization (WHO), TB has spread to every Corner of the globe.[7] As much as one-third of the World's population is currently infected and more Than 5000 people die from TB every day.[8] It is Estimated that between 2002 and 2020, Approximately 1000 million people will be newly Infected, over 150 million people will develop Diseases and 36 million will die of TB if proper Control measures are not established.[9] Tuberculosis (TB) is one of the oldest and most Pervasive, respiratory transmitted diseases in History.[10] WHO report, TB has spread to every Corner of the globe. As much as one-third of the World's population is currently infected, more Than any other infectious disease.[11]

Synthesis

Isoniazid, also known as isonicotinic acid hydrazide, is a relatively simple chemical structure that consists of pyridine ring and a hydrazine group attached at para position to the pyridine nitrogen. Isoniazid is prepared through the reaction of 4-cyano-pyridine and hydrazine hydrate in an aqueous alkaline medium at 100 C under reflux for 7 hours with subsequently crystallization in ethanol, thereby leading the desired compound with 62% of yield. (Figure 1).[12]

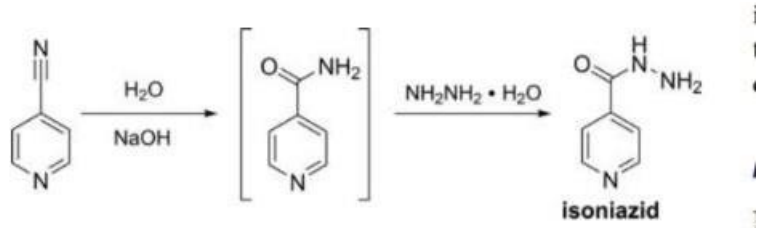

Figure 1. Synthesis of isoniazid.

Medication Profile

Other names and generic forms: rimitsid, tubazid, isonicotinic acid hydrazide, isonicotinoylhydrazi ne, INH, and so on. Pyridine-4-carbohydrazide is the CAS name. 54-85-3 is the CAS registry number. Formula for molecules: C6H7N3O, 137.14 molecular weight. Melting Point: 171.4°C Solubility: Freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol, and tetrahydrofuran; mildly soluble in acetone, water, and carbon tetrachloride. Category: Antitubercular Dosage: 300mg daily, or up to 1g twice per week. Description: Colorless crystals or white, crystalline powder; odorless. Storage: Keep well-closed, light-resistant containers.[13]

Mechanism of Action of isoniazid

Isoniazid is a prodrug that is changed into an active metabolite by the mycobacterial catalase-peroxidase enzyme. One of isoniazid's main functions is to inhibit the manufacture of mycolic acids, which are branching lipids that are joined to arabino galactan, a special polysaccharide, to form a portion of the cell wall of mycobacteria. Resistance maps to mutations in at least five separate genes (katG, isoniazidA, ahpC, kasA, and ndh), indicating a complex mode of action. IsoniazidA is the main pharmacological target, according to the overwhelming body of data. In fact, the isoniazidA gene product enoyl ACP reductase of fatty acid synthase II, which changes unsaturated fatty acids into saturated fatty acids in the mycolic acid biosynthesis pathway, binds to the catalase-peroxidase-activated isoniazid but not the prodrug. Since mycobacteria are the only ones that produce mycolicacids, and hence it inhibit the bacterial cell wall.[14]

Along with pyrazinamide and rifampicin, isoniazid (also known as Nicotinic Acid Hydrazide, INH, or H) is one of the preferred medications for the first therapy of tuberculosis. It works by preventing the tuberculosis bacterium from producing mycolic acid, which is a crucial component of its cell wall. In addition to giving the bacteria resistance to dehydration and chemical damage, mycolic acid als o stops hydrophobic antibiotics from having their intended effect. In addition, mycolic acid allows the bacterium to grow readily inside macrophages, effectively hiding it from the host's immune system. These reasons are vital for the selection of mycolic acid as a drug

target. Once circulated inthe bloodstream, the isoniazid prodrug is activated via a bacterial catalase-peroxidase enzyme, en-coded by KatG gene.[15]

Mechanism of Resistance to Isoniazid

Resistance to INH is seen when there is over production of the enzymes that are inhibited by INH. Mutation of inhA and Kat G enzymes result in resistance.16 Resistance bacteria do not allow drugpenetration. To prevent selection of mutants, Isoniazid should never be used alone, rather in combination with any other drug. It has no cross – resistance with other anti- tubercular drugs.[17]

Pharmacokinetics Of Isoniazid

Absorption

When taken orally or by a parent, isoniazid is easily absorbed. An oral dosage of 300 mg at fasting causes peak plasma concentrations of 3–8 μg/ml to occur 1-2 hours later. Antacids containing aluminum may prevent isoniazid from being absorbed properly.

DISTRIBUTION

Isoniazid easily permeates every bodily fluid and cell. It is believed that isoniazid does not bind to pl asma proteins very strongly. The infected tissue initially has a much lower concentration of the drug than the plasma and muscle, but the latter keeps the drug for a very long period and in much higher quantities than what is needed for bacteriostasis.

Metabolism

Tha plasma half- life of Isoniazide ranges from 1-4 h, those who are fast acetylators because of genetic variations, having short half -lives. The primary metabolic route is acetylation of Isoniazid to acetylisoniazid by N- acetyltransferase, form in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine, isonicotinic acid is conjugated with glycine to isonicotinyl glycine and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolized Isoniazid is conjugated to hydrazones.

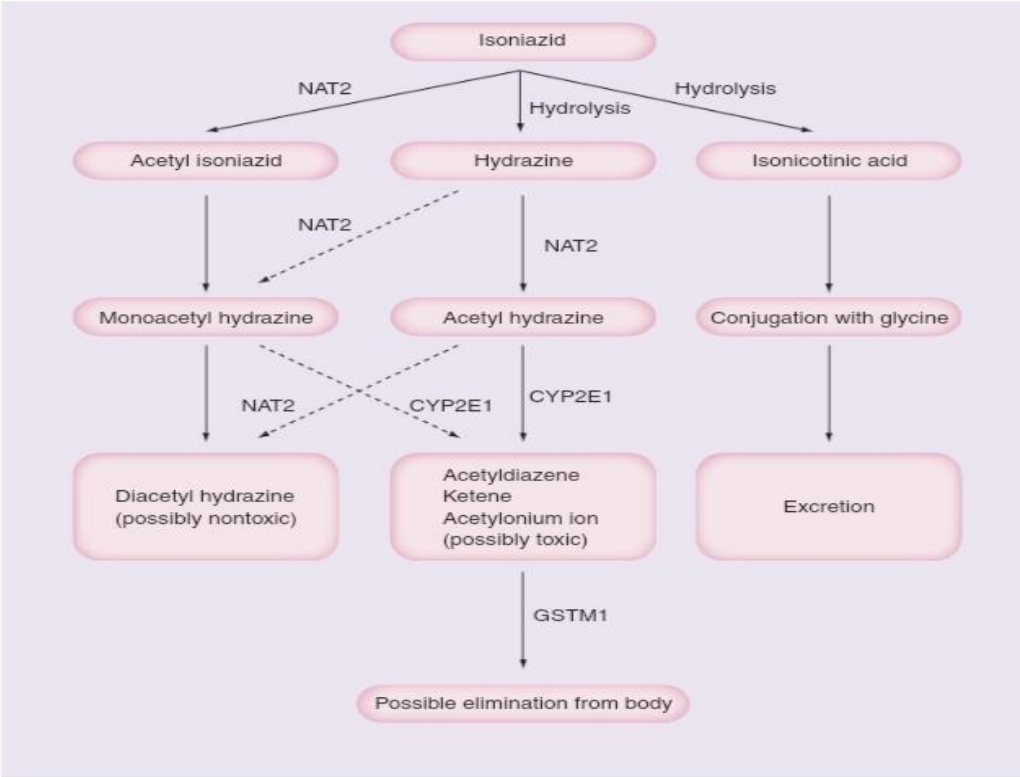

Figure 1: Suggested metabolic pathway of Isoniazid and metabolites by NAT2, CYP2E1 and GSTM1.[18]

Excretion

Acetylation of isoniazid is a genetically controlled process that is necessary for its excretion from the body. Renal excretion is the main mode. Within 24 hours, 75% to 95% of the isoniazid dosage is eliminated through urine, primarily in the form of metabolites. In 24 hours, more than 70% of a dosage in patients with normal renal function shows up in the urine. Of this quantity, 63% of the isoniazid i n slow acetylators was excreted in the urine as Nacetylisoniazid, whereas 93% was excreted in urine in rapid acetylators as Nacetylisoniazid (Gilbaldi, 1984). Additionally, little amounts of drugs are expelled in feces.[19]

Hepatotoxicity caused by Isoniazide

INH related clinically recognized hepatotoxicity tends to afflict 130% of populations generally, yet there is startling age dependency. According to reports, the incidence of liver injury is 1-2% in the middle aged group, 23% in the elderly, and extremely rare in youngsters under the age of 20. Patients with a lcohol misuse hepatitis B and C virus carriers and malnutrition have also been linked to a high prevalence of ATD hepatotoxicity. The majority of ATDs, including INH, RMP, and PZA, are toxic to the liver. Similar to INH, PZA can harm the liver in 15% of recipients, and in 2-3%

of these cases, jaundice may develop.[20]

Interaction

Aluminium hydroxide inhibits INH absorption. INH retards phenytoin, carbamazepine, diazepam, theophylline and warfarin metabolism by inhibiting CYP2C19 and CYP3A4, and may raise their blood levels. Since rifampin is an enzyme inducer, it's concurrent use counteracts the inhibitory effects of INH. However, the net effect on metabolism of many drugs is unpredictable. PAS inhibits INH metabolism and prolongs it's t1/2.

Adverse effects

INH is well tolerated by most patients. Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions) are the most important dose-dependent toxic effects. These are due to interference with production of the active coenzyme pyridoxal phosphate from pyridoxine, and it's increased excretion in urine. Pyridoxine given prophylactically (10 mg/ day) prevents the neurotoxicity even with higher doses. Prophylactic pyridoxine must be given to diabetics, chronic alcoholics, malnourished, pregnant, lactating and HIV infected patients, and when high dose INH is used. INH neurotoxicity is treated by pyridoxine 100 mg/ day. Hepatitis, a major adverse effect of INH, is rare in children, but more common in older people and in alcoholics (chronic alcoholicsm induces CYP2E1 which generate the hepatotoxic metabolite). INH must be stopped at the first sign of hepatotoxicity, which is due to dose-related damage to liver cells, and is reversible on stopping the drug. Other side effects are lethargy rashes,mild anaemia and arthralgia.[21]

Contraindications

Isoniazid can be given to individuals with stable liver disease, but the risk of drug buildup and drug induced hepatitis may increase. These patients should receive more frequent monitoring. It is not recommended for people who suffer severe hypersensitivity responses to isoniazid or any other com ponent of formulations. It is also not recommended for patients with druginduced hepatitis or who have previously experienced isoniazid-related hepatic injury.[22]

Therapeutic Uses

1) Most effective first line treatment against Mycobacterium tuberculosis.
2) Highly selective and potent tuberculostatic antibacterial agent.
3) It is Used to treat leprosy.
4) It is Used in immunonocompromised patient.[23]

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