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INTRODUCTION OF TUBERCULOSIS DISEASE AND CLASSIFICATION OF ANTI TUBERCULOSIS DRUGS

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SUMMARY

The arrangement of against tuberculosis (TB) drugs is imperative as it encourages the clinician to manufacture a fitting enemy of TB routine for multidrug-safe (MDR) and broadly medicate safe (XDR) TB cases that don't satisfy the criteria for the shorter MDR-TB routine. The World Health Organization (WHO) has as of late affirmed an amendment of the characterization of new enemy of TB drugs dependent on current proof on each medication. In the past WHO rules, the selection of medications depended on adequacy and poisonous quality in a stage down way, from gathering 1 first-line medications and gatherings 2– 5 second-line drugs, to bunch 5 drugs with conceivably restricted viability or constrained clinical proof. In the changed WHO arrangement, solely went for overseeing drug-safe cases, prescriptions are again recorded in progressive request from gathering A to amass D. In parallel, a conceivable future grouping is freely proposed. The point of this perspective article is to depict the development in WHO TB grouping (considering an autonomously proposed new arrangement) and late changes in WHO direction, while remarking on the contrasts between them. The most recent proof on the ex-gather 5 drugs is additionally talked about.

INTRODUCTION

TB is an airborne bacterial infection caused by *M. Tuberculosis* which affects any part of the body and most commonly the lungs. *M. Tuberculosis* is exposed to the air as droplet nuclei

from coughing, sneezing, shouting or singing of individuals with pulmonary or laryngeal TB. Transmission occurs through inhalation of these droplet nuclei which passes through the mouth or nasal cavities, the upper respiratory tract, bronchi and finally reaches the alveoli of the lungs.[1] Occasionally *Mycobacterium bovis*, transmitted through contaminated milk and *Mycobacterium africanum* may also cause the disease. The bacteria are transmitted from person to person through aerosolized droplet nuclei. Coughing, which generates infected droplets, is the most important mode of transmission of TB. Other strains of mycobacteria that causes TB are M. bovis, M. africanum, M. microti, M. avium and M. leprae.

History of Tuberculosis

Mycobacterium tuberculosis was first isolated in 1882 by Robert Koch who received Nobel Prize for this discovery in 1905.[2]

The history of tuberculosis (TB) mixtures with the history of humanity since TB is one of the oldest infectious diseases affecting mankind. Bone TB was identified in 4000 years old skeletons, from Europe and Middle East, as the cause of death, showing that this disease was already a widespread health problem back then.[3] In recorded history, Hippocrates writes about patients with wasting away associated with chest pain and coughing, frequently with blood in sputum. These symptoms allowed Hippocrates to diagnose TB, which at that time was called “consumption”. The frequency of descriptions of patients with these symptoms indicated that the disease was already well entrenched in ancient times.[4]

Worldwide, tuberculosis (TB) kills more young and middle-aged adults than any other infectious disease (WHO, 1999). Though it is curable and preventable, more than 5,000 people die of TB *every day* (2 to 3 million people per year) (WHO, 1999). TB often strikes the most vulnerable members of society and, if left untreated, causes its victims to lose weight, weaken, and eventually waste away (Ryan, 1993). TB disproportionately affects the indigent and other marginalized groups of society in whom unequal susceptibility patterns have long been recognized (Dubos & Dubos, 1952).[5]

Currently, more than one-third of the world’s population is infected with *Mycobacterium tuberculosis* (*M. tuberculosis*). According to the latest report released by the WHO, in 2009, there were 9.4 million incident cases, 14 million prevalent cases, 1.3 million deaths among HIV-negative people and 0.38 million deaths among HIV-positive people [3]. In addition to

these already frightening numbers, people who are latently infected constitute the hidden reservoir of the disease from which new cases of active disease can emerge.[6]

Diagnosis of Tuberculosis

There are five key components of a complete evaluation of TB disease.

These are[1]:

(I) Medical history taking

(II) Physical examination

(III) Test for *M. Tuberculosis* infection

(IV) Chest radiograph

(V) Bacteriologic examination of clinical specimens

The most widely used diagnostic method for TB is microscopic examination of stained smears of sputum, while sputum cultures usually confirm the diagnosis. Chest radiographs are commonly used to assist in diagnosis. The tuberculin skin test is used to diagnose LTBI (CDC, 1995a, 2000).[7]

Latent Infection

Screening and treatment for latent *M. tuberculosis* infection are indicated for groups in which the prevalence of latent infection is high (e.g., foreignborn persons from regions in which tuberculosis is endemic), those in whom the risk of reactivated disease is high (e.g., patients with HIV infection or diabetes and patients receiving immunosuppressive therapy), and those with both factors (e.g., recent contacts of patients with tuberculosis).[8]

Latent infection can be diagnosed with either a tuberculin skin test or an interferon-gamma release assay. Specific guidelines from the Centers for Disease Control and Prevention in the United States the National Institute for Health and Clinical Excellence in the United Kingdom and the European Centre for Disease Prevention and Control recommend the use of the interferon- gamma release assay and tuberculin skin test for screening for latent *M. tuberculosis* infection in various age and risk groups. The tuberculin skin test is less expensive and is therefore preferred in low-income regions. It is as sensitive as the interferon-gamma release assay but less specific.[9]

Active Tuberculosis

Sputum microscopy and culture in liquid medium with subsequent drug-susceptibility testing are currently recommended as standard methods for diagnosing active tuberculosis. The use of solid culture medium is more cost-effective in resource poor countries. Interferon-gamma release assays and tuberculin skin tests have no role in the diagnosis of active disease. Nucleic acid amplification tests, imaging, and histopathological examination of biopsy samples supplement these evaluations. In resource-constrained settings with a high prevalence of tuberculosis and HIV infection, an estimated 30% of all patients with tuberculosis and more than 90% of those with multidrug- resistant and extensively drug-resistant tuberculosis do not receive a diagnosis.[8]

A new molecular diagnostic test called Xpert MTB/RIF assay detects *M. tuberculosis* complex within 2 hours, with an assay sensitivity that is much higher than that of smear microscopy. In HIV infected patients, the test has a rate of case detection that is increased by 45%, as compared with smear microscopy. This molecular assay has the potential to improve the performance of national tuberculosis programs and is currently being implemented in district-level laboratories in 67 countries with a high prevalence of tuberculosis. It is available in Europe and is being examined for approval in the United States.[8]

Treatment of Tuberculosis

The first experimental evidence of the potential efficacy of new antituberculosis drugs was obtained in 1940 when a dapsone-derivative compound, known as promin, was administered to a sample of guinea pigs. However, that sulfonamide was never given to humans.[10]

Streptomycin was the first drug used for the treatment of tuberculosis.13-15 It was isolated in 1944 by Selman Abraham Waksman16 and he was awarded the Nobel Prize for this discovery in 1952. Two years later, in 1946, Jorgen Lehmann discovered para aminosalicylic acid (PAS) as an effective TB drug.[2]

The first trial was performed comparing the efficacy of streptomycin and Para amino salicylic acid both as mono therapy 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. 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.[11]

Finally, in 1980, pyrazinamide was introduced into the anti-TB treatment, which could be reduced further to only six months. 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.[12] 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.[13]

Tuberculosis treatment consists of a multi-drug regimen with duration of 6 to 8 months. The preferred first-line drugs are isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB). When the bacterial strain becomes resistant to one or more of these drugs, second-line drugs are used. These include streptomycin, kanamycin, fluoroquinolones, ethionamide, and p-aminosalicylic acid. Generally, second-line drugs are less effective and more toxic compared to the first-line drugs. In this paper, we will be primarily discussing the metabolism and associated toxicity of first-line antituberculosis drugs.[14]

Classification of Antitubercular Drugs

The antitubercular drugs are classified as first line, second line and third line drugs based on their efficacy, side effects, toxicity, availability and cost.

The first-line antitubercular drugs are

- Streptomycin,
- Rifampicin,
- Ethambutol,
- Isoniazid and
- Pyrazinamide.

Tuberculosis can be cured by using first line drugs with the success rate of up to 95%. If the treatment fails because of the bacterial resistance or intolerance to one or more drugs, second line drugs are used.

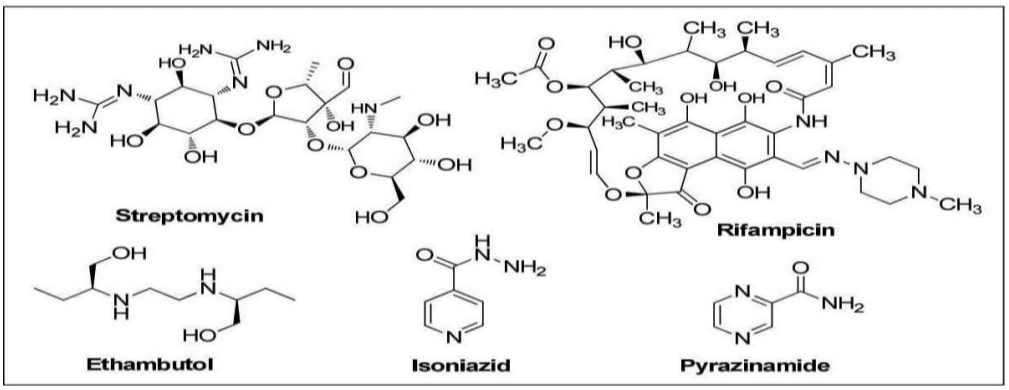


Fig. 1: First line anti-tubercular drugs.

There are six classes of second line drugs used for the treatment of TB.

- Amino glycosides: eg amikacin, kanamycin
- Polypeptides: eg capreomycin, viomycin
- Fluoroquinolones: eg ciprofloxacin, gatifloxacin, moxifloxacin
- Thioamides: eg ethionamide, prothionamide
- Isoxazolidinone: eg cycloserine
- Salicylic acid: eg p-aminosalicylic acid

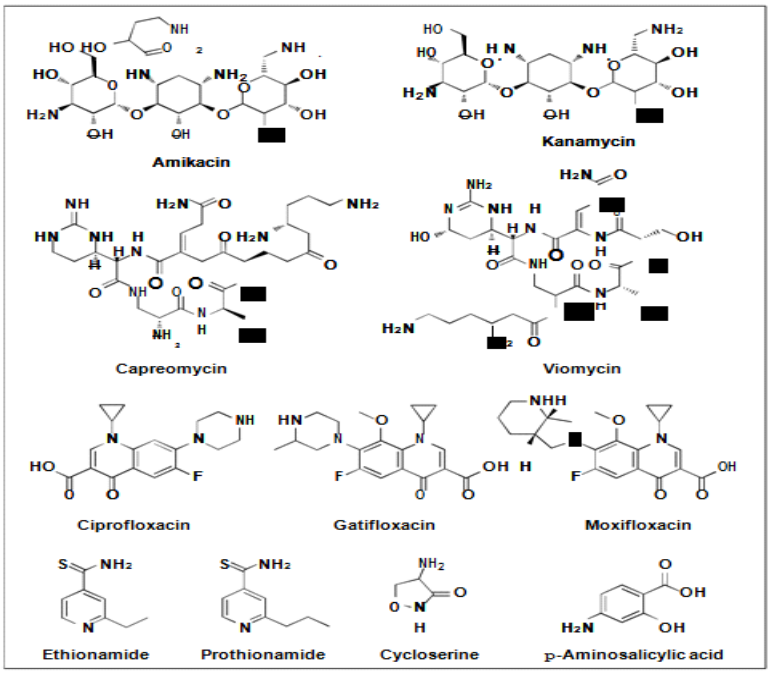


Fig. 2: Second line anti-tubercular drugs.

Second line drugs are less effective, more toxic and more expensive than the first line agents. Other drugs which are not very effective and not included in the WHO list are called third line drugs. These drugs include rifabutin, macrolides (clarithromycin), linezolid, thioacetazone, thioridazine, arginine etc.

Classification of new antitubercular drugs

The World Health Organisation (WHO) has recently updated the classification of new anti-tuberculosis drugs.4,25 Previous World Health Organisation (WHO) guidelines classified anti-TB drugs into five main groups, based on safety and effectiveness considerations. This classification originated in 2006, updated in 2008, 2011 and, finally, in 2016 based on new evidence, mainly from the former group 5 drugs.[15-17]

WHO categorisation of second-line antituberculosis drugs recommended for the treatment of rifampicin resistant and multidrug-resistant tuberculosis.

Group A: fluoroquinolones

- Levofloxacin
- Moxifloxacin
- Gatifloxacin

Group B: second-line injectable agents

- Amikacin
- Capreomycin
- Kanamycin
- (Streptomycin)

Group C: other core second-line agents

- Ethionamide/prothionamide
- Cycloserine/terizidone
- Linezolid
- Clofazimine

Group D: add-on agents (not part of the core multidrug-resistant tuberculosis regimen)

D1

- Pyrazinamide
- Ethambutol

- High-dose isoniazid

D2

- Bedaquiline
- Delamanid

D3

- Para-aminosalicylic acid
- Imipenem plus cilastatin (requires clavulanate)
- Meropenem (requires clavulanate)
- Amoxicillin plus clavulanate
- (Thioacetazone)

Isiniazid: First Line Antitubercular Drugs

Tuberculosis can be cured by using first line drugs with the success rate of up to 95%. If the treatment fails because of the bacterial resistance or intolerance to one or more drugs, second line drugs are used.

Isoniazid (INH) is a hydrazide derivative of isonicotinic acid. It was first synthesized in 1921 by Meyer and Malley from ethyl isonicotinate and hydrazine and its activity against tuberculosis was first reported in the late 1940s.

Isoniazid was introduced in 1952 as an anti-TB agent and it remains, together with rifampicin, as the basis for the treatment of the disease. Unlike rifampicin, isoniazid is only active against metabolically-active replicating bacilli.[18]

Drug Profile[20]

Generic and additional names: isonicotinic acid hydrazide; isonicotinoylhydrazine; isonicotinylhydrazine; INH; rimitsid; tubazid

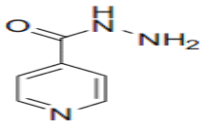
CAS name : pyridine-4-carbohydrazide

CAS registry number : 54-85-3

Molecular formula : C6H7N3O

Molecular weight : 137.14

Structure :



Melting point : 171.4°C

Solubility : Freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol, tetrahydrofuran; slightly soluble in acetone, water, carbon tetrachloride

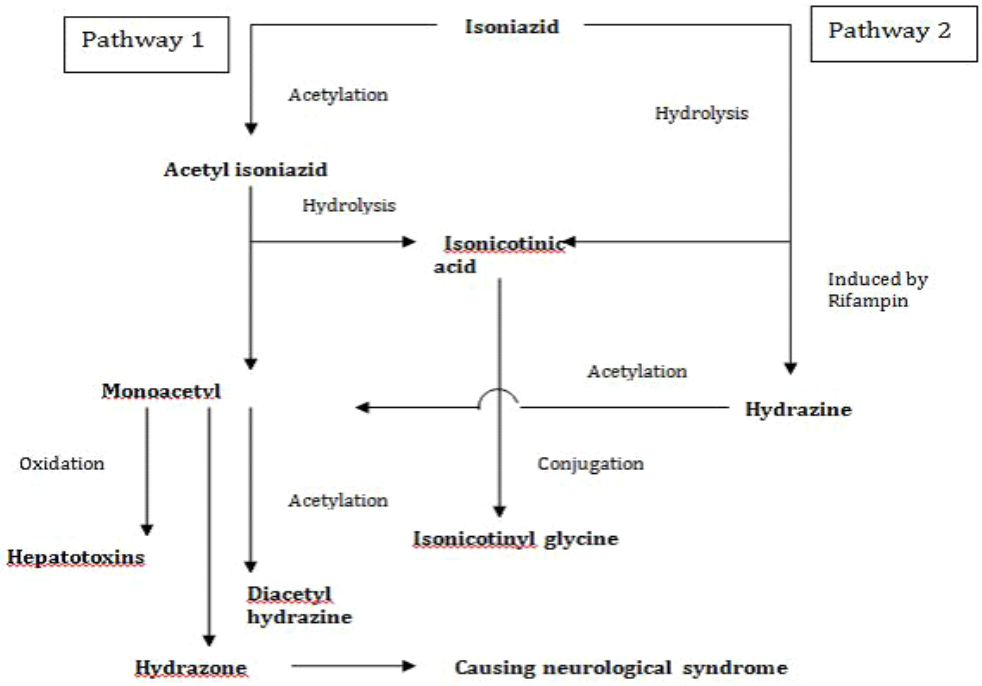
Category : Antitubercular

Dose : 300mg daily or up to 1g twice weekly.

Description : Colourless crystals or white, crystalline powder; odourless.

Storage : Store in well-closed, light- resistant containers.

INH is isonicotinyl hydrazine (arylhydrazine). It is rapidly absorbed when orally dosed and attains peak plasma levels within one to two hours post administration. It is mainly metabolized in the liver, primarily through the N-acetyltransferase (NAT) enzyme system. In fact, discovery of INH as an antituberculosis drug had triggered the detail study of the NAT system.[14]



Mechanism of action

Isoniazid is a prodrug and must be activated by the M. tuberculosis catalase-peroxidase enzyme KatG; the activation of isoniazid produces oxygen-derived free radicals (superoxide, hydrogen peroxide, and peroxynitrite) and organic free radicals that inhibit the formation of mycolic acids of the bacterial cell wall, causing DNA damage and, subsequently, the death of the bacillus. The most common mechanism of resistance to isoniazid consists of KatG

mutations, which decrease the activity of isoniazid and prevent the prodrug from being converted into its active metabolite.[19]

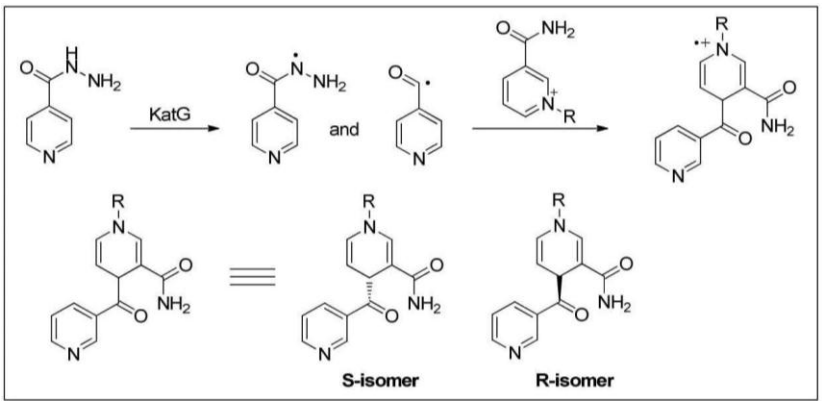


Fig.3: Formation of INH-NAD adduct: Mechanism of action of INH.

Mechanism of Resistance to Isoniazid

M. tuberculosis resistance to isoniazid is a complex process and is associated in mutations in several genes including katG, acpM, inhA, kasA and ahpC. Isoniazid activated by the catalase-peroxidase enzyme (katG) interferes with the synthesis of essential mycolic acids by inhibiting NADH dependent enoyl-acyl carrier protein reductase enzyme (inhA). The most common cause for isoniazid resistance is mutations in the activating enzyme katG and mutations in the target gene inhA. More than 80% of INH-resistant clinical M. tuberculosis isolates have mutations in katG, reducing the ability of the catalaseperoxidase to activate the INH.[21]

Metabolism and Toxicity of Isoniazid

Isoniazid is metabolized in liver mainly by acetylation with the hepatic enzyme Nacetyltransferase- 2 (NAT2). Isoniazid is acetylated into acetylisoniazid and then hydrolyzed into acetylhydrazine and isonicotinic acid. Acetylhydrazine is either hydrolyzed to hydrazine, or acetylated into diacetylhydrazine. A small part of isoniazid is directly hydrolyzed into isonicotinic acid and hydrazine. Acetylhydrazine was thought to be toxic metabolite of isoniazid but recent studies suggest that hydrazine is most likely to be the cause of isoniazid induced hepatotoxicity.

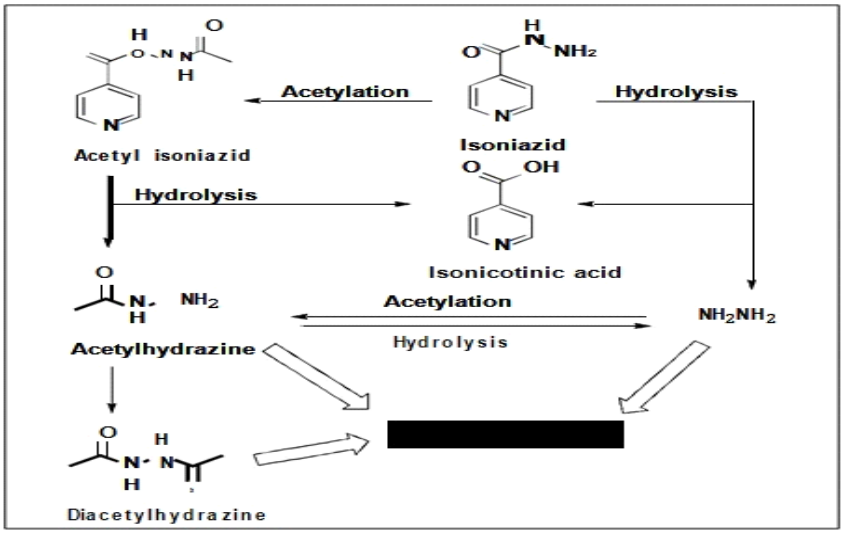


Fig.4: Isoniazid: Metabolism and Toxicity.

The rate of acetylation is genetically determined and can be divided into slow and fastmacetylators. In slow acetylates, more isoniazid is left for direct hydrolysis into hydrazine and also the accumulated acetylhydrazine can be converted into hydrazine leading to an increased risk of toxicity. Huang et al demonstrated that slowly acetylates have more than two-fold risk of developing anti-tuberculosis drug-induced hepatotoxicity (ATDH) compared with fast acetylators. Fast acetylation leads to higher blood levels of the toxic metabolite acetylisoniazid.

PHARMACOKINETICS OF ISONIAZID

Absorption

Isoniazid is readily absorbed when administered either orally or parentally. Peak plasma concentrations of 3-8 µg/ml develop 1-2 h after fasting dose of 300 mg orally. Aluminium containing antacids may interfere with the absorption of isoniazid.

Distribution

Isoniazid diffuses readily into all body fluids and cells. Isoniazid is not considered to be bound appreciably to plasma proteins. The concentration of the drug is initially higher in the plasma and muscle than in the infected tissue, but the latter retains the drug for long time in quantities well above those required for bacteriostasis.

Metabolism

The plasma half-life of isoniazid 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 monacetylhydrazine, isonicotinic acid is conjugated with glycine to isonicotinyl glycine and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolized isoniazid is conjugated to hydrazones.

Excretion

Elimination of isoniazid from the body is dependent upon its genetically controlled rate of acetylation. Excretion is primarily renal. From 75% to 95% of dose of isoniazid is excreted in the urine within 24 h, mostly as metabolites. In patients with normal renal function, over 70% of a dose appears in the urine in 24 h. Of this amount, 93% of the isoniazid excreted in urine in fast acetyltors in the form of N-acetylisoniazid and 63% in slow acetylators as N-acetylisoniazid (Gilbaldi, 1984). Small amounts of drug are also excreted in faeces.

Drug-drug interactions

Isoniazid interacts with the cytochrome P-450 system, especially CYP2E1, where it shows a biphasic inhibition induction; it causes increases in serum concentrations of various drugs, especially phenytoin and carbamazepine, increases the effects of warfarin and theophylline, inhibits metabolism of benzodiazepines, and inhibits monoamine oxidase and histaminases. Isoniazid should not be administered with food, as studies have shown that this significantly reduces its bioavailability.

ADVERSE EFFECTS OF ISONIAZID

Central Nervous System (CNS) effects: Peripheral neuropathy is the most common CNS related toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics), and is usually preceded by paraesthesias of the feet and hands. The incidence is higher in “slow acetylators”. Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.

***Hepatic effects*:** Isoniazid does carry a specific warning of the potential for liver toxicity. Liver toxicity and hepatitis risks are increased with concomitant use of carbamazepine, phenobarbital, rifampicin, and alcohol abuse. Elevated serum transaminase (SGOTSGPT), bilirubinaemia, bilirubinuria, jaundice, and occasionally severe and sometimes fatal hepatitiscan occur with normal dosing regimens. The common prodromal symptoms of hepatitis are anorexia nausea, vomiting, fatigue, malaise, and weakness. Mild hepatic

dysfunction, evidenced by mild and transient elevation of serum transaminase levels appears in the first 1-3M of treatment but can occur at any time during therapy. In most instances enzyme levels return to normal, and generally there is no necessity to discontinue medication during the period of mild serum transaminase elevation. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2.3% of those over 50 years of age.

***Gastrointestinal effects*:** Nausea, vomiting, epigastric distress and dark urine can occur but are rare. Haematological effects: agranulocytosis; hemolytic, sideroblastic, or aplastic anaemia, thrombocytopenia; and eosinophilia can occur.

***Endocrine and metabolic*:** Pyridoxine deficiency, pellagra, hyperglycaemia, acidosis and gynecomastia can occur.

***Hypersensitivity*:** Fever, skin rashes, lymphadenopathy and vasculitis can occur.

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