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2.5.5 OVERVIEW OF SAFETY

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2.5.1 Product Development Rationale

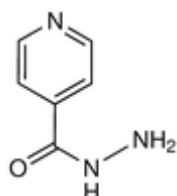
Nearly one-third of the global population, i.e. two billion people, is infected with Mycobacterium tuberculosis and are at risk of developing tuberculosis (TB). More than eight million people develop active TB every year, and about two million die. More than 90% of global TB cases and deaths occur in the developing world, where 75% of cases are in the most economically productive age group (15-54 years).

Co-infection with the human immunodeficiency virus (HIV) significantly increases the risk of developing TB. Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have witnessed a profound increase in the number of TB cases, with reported incidence rates increasing two- or threefold in the 1990s.

At the same time, multidrug resistance, which is caused by poorly managed TB treatment, is a growing problem of serious concern in many countries around the world.

Since its introduction in 1952, isoniazid (isonicotinyl hydrazide, INH) has been the major drug for the prevention and treatment of tuberculosis. INH is available worldwide, is inexpensive and is generally well tolerated.

INH is chemically, isonicotinohydrazide and has the following structural formula:



$C_6H_7N_3O = 137.1$

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INH is mainly available in the oral dosage form though the drug is administered intramuscularly or intravenously in rare cases.

INH is a component of all TB chemotherapeutic regimens currently recommended by WHO. INH is also used alone occasionally to prevent:

- transmission to close contacts at high risk of disease;
- progression of infection to primary complex in recently infected, asymptomatic individuals;
- development of active TB in immunodeficient individuals

INH is generally well tolerated. Peripheral neuritis and hepatotoxicity are the most frequently observed adverse effects of INH.

Despite the development of other drugs, INH remains a most valuable drug for treatment of tuberculosis.

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2.5.2 Overview of Biopharmaceutics

2.5.2.1 Bioavailability

2.5.2.1.1 Pharmacokinetic data of substance in animals

The mean pharmacokinetic parameters of INH in male Wistar rats administered INH (100mg/kg/day) for 21 days was as under: (⁴ *Baldan et al., 2007*)

Absorption half-life ($t_{1/2a}$)	0.4 h
Distribution half-life ($t_{1/2\alpha}$)	1.4 h
Elimination half-life ($t_{1/2\beta}$)	3.4 h
Area under curve 0 to 24 h (AUC)	146.36 $\mu\text{gh ml}^{-1}$
Apparent volume of distribution (V_d/F)	3.32 l/kg

Male New Zealand White rabbits were given 100 mg/kg of ¹⁴C-INH per day for 7 days. Absorption and elimination of INH was rapid since the peak ¹⁴C level was attained by 1 hr and the $t_{1/2}$ of elimination was about 2.6 hr. By 12 hr about 68% of the dose was recovered in the urine. The major metabolite excreted in the urine was isonicotinic acid (INA) which accounted for about 40% of the dose followed by acetylisoniazid (AcINH) at about 15%. The relatively high proportion of INA excreted by the rabbit compared to the rat and human is attributed to a high level of amidase in the rabbit, and is suggested as a possible explanation for the rabbit's sensitivity to INH induced hepatotoxicity. (²⁰ *Thomas et al., 1981*)

The absorption, distribution, and excretion characteristics of INH in the dog appear to be similar to those reported in man. (¹⁴ *Rubin & Burke, 1953*)

2.5.2.2 Summary of bioavailability studies

2.5.2.2.1 Comparative bioavailability data

Not applicable

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2.5.2.2.2 Bioavailability of drug following single dosing in healthy volunteers

INH is readily absorbed after oral administration and after intramuscular injection. Peak concentrations of about 3 to 7 µg/mL appear in blood 1 to 2 hours after an oral fasting dose of 300 mg. The rate and extent of absorption of INH is reduced by food. INH is not considered to be bound appreciably to plasma proteins and distributes into all body tissues and fluids, including the CSF. It appears in fetal blood if given during pregnancy and is distributed into breast milk. (⁹ *Martindale, 2009*)

The plasma half-life for INH ranges from about 1 to 6 hours, with shorter half-lives in fast acetylators. The primary metabolic route is the acetylation of INH to acetylisoniazid by N-acetyltransferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotiny glycine (isonicotinuric acid) and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised INH is conjugated to hydrazones. The metabolites of INH have no tuberculostatic activity and, apart from possibly monoacetylhydrazine, they are also less toxic. The rate of acetylation of isoniazid and monoacetylhydrazine is genetically determined and there is a bimodal distribution of persons who acetylate them either slowly or rapidly. Ethnic groups differ in their proportions of these genetic phenotypes. When INH is given daily or 2 or 3 times weekly, clinical effectiveness is not influenced by acetylator status. (⁹ *Martindale, 2009*)

In patients with normal renal function, over 75% of a dose appears in the urine in 24 hours, mainly as metabolites. Small amounts of drug are also excreted in the faeces. INH is removed by haemodialysis. (⁹ *Martindale, 2009*)

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2.5.3 Overview of Clinical Pharmacology

2.5.3.1 Pharmacokinetics

2.5.3.1.1 Absorption

Orally ingested INH is rapidly and completely absorbed provided there is no interference from food or drugs in the gastrointestinal tract. Peak plasma concentrations of 3 - 7 mg/L are achieved 1 - 2 hr after oral administration of normal therapeutic dose to adults. Its bioavailability is reduced, however, by high carbohydrate meals and by various antacids. (¹⁷ *Sir Colin Dollery, 1991*)

INH undergoes appreciable presystemic (first pass) metabolism in the wall of the small intestine and liver, resulting in concentrations in the plasma of rapid acetylators which are half those in slow acetylators after normal doses (300 mg) of the drug. There is no measurable difference in the peak INH concentrations in rapid and slow acetylators after intravenous administration. (¹⁷ *Sir Colin Dollery, 1991*)

INH does not accumulate appreciably with multiple daily doses, hence samples obtained as early as the first day of therapy will reflect steady state values. (¹¹ *Peloquin et al., 1997*)

In a single-dose study in healthy fasting males, the extent of absorption (as measured by area under the plasma concentration-time curve) of isoniazid, rifampicin, or pyrazinamide in dosages of 250 mg, 600 mg, or 1500 mg, respectively, was similar whether the drugs were administered individually as capsules (rifampicin) and tablets (isoniazid and pyrazinamide) or as a fixed combination containing isoniazid 50 mg, rifampicin 120 mg, and pyrazinamide 300 mg per tablet. (² *AHFS, 2008*)

2.5.3.1.2 Distribution

INH is distributed into all body tissues and fluids. CSF concentrations of the drug are reported to be 90–100% of concurrent plasma concentrations. INH is not substantially bound to plasma proteins INH readily crosses the placenta. Similar levels are found in

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maternal and cord blood while higher levels are present in the amniotic fluid. INH is distributed into milk in concentrations approximately equal to maternal plasma concentrations. (² *AHFS, 2008*; ¹² *Preziosi, 2007*) It is estimated that 0.75 to 2.3% of the dose is excreted into breast milk in 24 hours. This corresponds to 6-20% of a usual therapeutic paediatric dose. (⁸ *IPCS INCHEM, 1999*)

INH is found in saliva, pleural and peritoneal exudates and in fluid lining the bronchi and pulmonary alveoli. Measurement of salivary INH concentrations can be used as a noninvasive alternative to the measurement of plasma concentrations. INH penetrates the pulmonary alveolar cells by a process of passive diffusion, reaching concentrations similar to those found in the plasma. (¹² *Preziosi, 2007*)

INH is distributed in total water with a mean apparent distribution volume of 0.6 to 0.75 L/kg. The volume of distribution is unrelated to acetylator status or age. High quantities of the drug have been found in lung and skin which suggests these organs may serve as storage depots. (¹⁷ *Sir Colin Dollery, 1991*; ⁷ *Drugdex, 2006*)

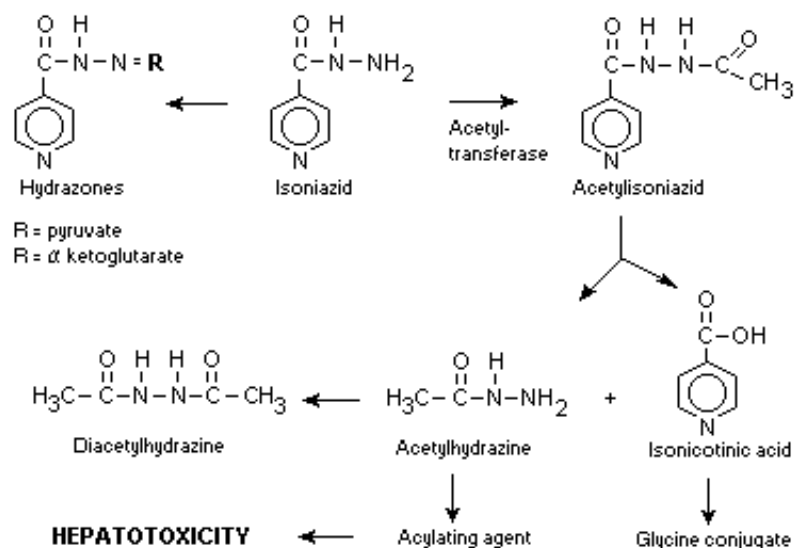
2.5.3.1.3 Metabolism and excretion

The primary metabolic route is the acetylation of INH to acetylisoniazid by N-acetyltransferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinuric acid) and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised INH is conjugated to hydrazones. The metabolites of INH have no tuberculostatic activity and, apart from possibly monoacetylhydrazine, they are also less toxic. (⁹ *Martindale, 2009*)

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Fig 1 Metabolites of INH (⁸ *IPCS INCHEM, 1999*)



The rate of acetylation of INH and monoacetylhydrazine is genetically determined and is subject to individual variations. Although it may be influenced by age and weight it is usually constant for each person. Two groups of people can be distinguished: slow acetylators and fast acetylators. The phenotype of slow acetylators is an autosomal recessive trait and results from a relative deficiency of the hepatic enzyme N-acetyltransferase. The incidence of slow acetylators taken from various sources estimates 45-55% in Americans, 60% in Europeans, 50-65% in Caucasians, Blacks, South Indians, Mexicans. The incidence of fast acetylators is 80-90% in Eskimos, Japanese and Chinese. (⁸ *IPCS INCHEM, 1999*)

Pharmacokinetic data indicate that for fast acetylators the median C_{max} of INH (after administration of a dose of 250 mg) is 48 times the MBC (Minimum Bacterial Concentrate and concentrations in serum remain above the MBC until ~ 8 h postdosing. For slow acetylators, the median C_{max} of INH (after administration of a dose of 250 mg) is 73 times the MBC and concentrations in serum remain above the MBC until ~ 22 h postdosing. Somewhat higher values would be seen with the standard 300-mg doses. Despite these differences, both acetylator types have roughly equivalent responses to treatment in clinical trials except when the dosing interval is extended to once weekly. In that seldom used regimen, slow acetylators had better responses. (¹¹ *Peloquin et al., 1997*)

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Microsomal metabolism of monoacetylhydrazine in animals results in production of a reactive acylating species capable of covalently binding with tissue macromolecules (i.e., liver protein) and subsequently causing hepatic necrosis. Although attempts have been made to correlate acetylator phenotype with risk of INH-induced hepatotoxicity, published reports are equivocal, with some showing an association with slow inactivators and others showing an association with rapid inactivators. It has been suggested that acetylator phenotype is probably not a major determinant of INH-induced hepatotoxicity, since the rate of acetylation of toxic monoacetylhydrazine to nontoxic diacetylhydrazine is also determined by acetylator phenotype. Thus, although rapid inactivators form more monoacetylhydrazine, they also inactivate it more rapidly. (² *AHFS*, 2008)

Numerous studies have demonstrated that the metabolism of INH varies widely in different individuals, with half-lives of 80 ± 30 minutes for rapid acetylators and 180 ± 70 minutes for slow acetylators. The plasma half-life may be prolonged in patients with impaired hepatic function or severe renal impairment. The half-life is 8 to 17 hours in patients with end stage renal disease. (⁷ *Drugdex*, 2006)

In adults with normal renal function, approximately 75–96% of a 5-mg/kg oral dose of INH is excreted in urine within 24 hours as unchanged drug and metabolites. 93% of the INH excreted in the urine may occur as the acetylated form in fast acetylators and 63% in slow acetylators, with the remainder, in both cases, occurring as the free or conjugated form. Small amounts of the drug are also excreted in saliva, sputum, and feces. INH is removed by hemodialysis or peritoneal dialysis. (² *AHFS*, 2008; ²² *Toxnet*)

Table 1. Principal pharmacokinetic properties of INH in man (²³ *Weber et al.*, 1979)

Elimination half-life	Wide individual variability; bimodal and determined by acetylator status
Absorption	Rapid and complete both orally and parenterally; plasma levels peak 1 to 2 hours after oral ingestion
Distribution	Total body water; intra- and extracellular
Plasma protein binding	Not appreciably bound
Metabolism	Wide individual variability; elimination is principally dependent on genetically controlled polymorphic liver N-acetyltransferase
Renal excretion	Elimination is virtually independent of renal function

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2.5.3.1.4 Effect of age and disease on pharmacokinetics

Elderly

Age has been shown to be an insignificant factor in the acetylator phenotype of an individual and the INH half-life. Thus, it has been concluded that there are no pharmacokinetic grounds for reducing the dosage of INH in the elderly. It should be noted, however, that age appeared to be an important factor in determining the risk of hepatotoxicity to INH, ranging from rare occurrences in individuals under 20 to a frequency of 2.3 % in patients over 50 years. (²³Weber *et al.*, 1979)

Infants and Children

The pharmacokinetics of INH was studied in children (0-196 months old) according to their acetylator phenotype. The mean apparent plasma clearance was significantly lower, the mean apparent volume of distribution higher and the half-life longer in the slow acetylator group than in the fast acetylator group as shown below: (¹³Rey *et al.*, 2001)

Acetylator phenotype	Apparent plasma Clearance (L/h/kg)	Apparent volume of distribution (L/kg)	Half-life (h)
Slow acetylators	0.298 ± 0.099	1.56 ± 0.65	3.88 ± 1.89
Fast acetylators	0.528 ± 0.234	1.06 ± 0.45	1.64 ± 1.1

Younger children eliminate INH faster than older children and, as a group, faster than adults, and require a higher mg/kg body weight INH dose to achieve serum concentrations comparable to adults. It is, therefore, suggested that young children less than 5 years of age should receive an INH dose of at least 10 mg/kg to ensure that the faster acetylators of INH are exposed to adequate serum concentrations of INH. (¹⁵Schaaf *et al.*, 2005)

Following oral INH (10 mg/kg and 20 mg/kg), in children with tuberculous meningitis, cerebrospinal fluid INH levels were significantly lower in fast acetylators than in slow acetylators. (⁷Drugdex, 2006)

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2.5.3.1.5 Pharmacokinetic Studies in Special Populations

2.5.3.1.5.1 Kinetics in patients with chronic renal failure

The clearance of INH is dependent to only a small degree on the status of renal function, but patients who are slow inactivators of the drug may accumulate toxic concentrations if their renal function is impaired. (²² *Toxnet*)

In patients with a creatinine clearance of less than 10 ml/min the daily dose of INH should be decreased by 50%. However, normal doses has also been recommended to be given to all patients including patients who are anuric. (⁷ *Drugdex, 2006*)

In a study of 6 patients with renal failure receiving INH 300 mg/day orally for 2 weeks, no progressive accumulation of INH drug concentration was observed. Customary doses of INH for TB therapy can be utilized for patients with renal failure. (⁷ *Drugdex, 2006*)

2.5.3.1.5.2 Kinetics in patients with hepatic dysfunction

Normal healthy subjects and patients with chronic liver disease were administered 600 mg INH as a single dose. Serum levels and half-life of INH were significantly higher in patients with chronically impaired liver. In a similar study INH 600 mg and rifampicin 600 mg were given together to healthy subjects and patients with chronic liver disease over a period of one week. No changes in serum INH concentrations were observed between day 1 and day 7 in the healthy subjects, whereas a significant increase was observed in the patients. No significant changes in the half-life of INH were observed. The results also showed a trend towards decrease in the serum levels of rifampicin of the healthy subjects and a trend towards increase in the patients with chronic liver disease on day 7 of treatment. (¹ *Acocella et al., 1972*)

Liver disease may prolong the half-life of INH; however, this effect is less significant than the genetic predisposition for rapid or slow acetylation. It is suggested that INH therapy for the prevention of tuberculosis be deferred in patients with acute hepatic disease. (⁷ *Drugdex, 2006*)

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2.5.3.2 Pharmacodynamics

2.5.3.2.1 Clinical review of the pharmacodynamic effects in vitro and in vivo

INH is a hydrazide derivative that is the mainstay of the primary treatment of pulmonary and extrapulmonary tuberculosis. It is bactericidal in vitro and in vivo against actively dividing tubercle bacilli; it is less active against non-dividing tubercle bacilli being only bacteriostatic. (⁹ *Martindale, 2009*; ¹⁷ *Sir Colin Dollery, 1991*)

INH enters the mycobacterial cell by passive diffusion. INH itself is not toxic to the bacterial cell, but acts as a prodrug and is activated by KatG encoded mycobacterial catalase peroxidase enzyme. The activation of INH by KatG generates a reactive isonicotinoyl radical, which forms adducts with cellular pyridine nucleotide coenzymes, NAD⁺ and NADP⁺. The adducts thus formed are potential inhibitors of lipid and nucleic acid biosynthetic sequence. A direct role of some INH-derived reactive species such as nitric oxide in inhibiting mycobacterial metabolic enzyme has also been shown. The inhibition of both cell wall lipid and nucleic acid synthesis, together with metabolic enzyme inhibition by INH-derived nitric oxide makes INH very effective because it attacks multiple targets. (²¹ *Timmins & Deretic, 2006*; ³ *Argyrou et al., 2007*)

Significant evidence supports the concept that INH blocks the synthesis of cell-wall mycolic acids, the major components of the envelope of M tuberculosis Fig 1. (¹⁹ *Somoskovi et al., 2001*)

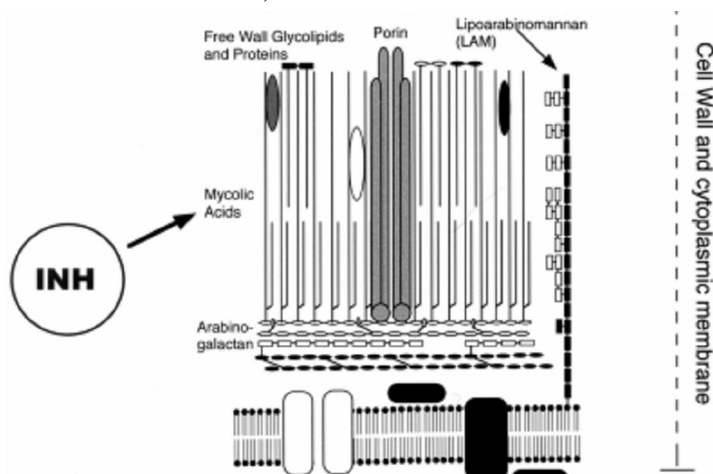


Fig 2. Sites of action of INH

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One of the intracellular targets for the drug is the fatty-acid enoyl-acyl carrier protein reductase (InhA), an enzyme involved in synthesis of mycolic acids. Because mycolic acids are unique to mycobacteria, this action would explain the high degree of selectivity of the antimicrobial activity of INH. (¹⁹ *Somoskovi et al., 2001*; ²² *Toxnet*)

Inhibition of mycolic acid results in loss of acid-fastness and disruption of the bacterial cell wall. INH is active against susceptible bacteria only when they are undergoing cell division. Susceptible bacteria may undergo 1 or 2 divisions before multiplication is arrested. (² *AHFS, 2008*)

INH is a highly specific agent and is active only against organisms of the genus *Mycobacterium*. INH is active in vitro and in vivo against *M. tuberculosis*, *M. bovis* and some strains of *M. kansasii*. In vitro, the minimum inhibitory concentration (MIC) for most susceptible mycobacteria is 0.02–0.2 mcg/mL in Lowenstein-Jensen media. (*AHFS, 2008*) Using radiometric techniques the MIC of INH for *M. tuberculosis* has been shown to be 0.025 to 0.05 mg/ml and the minimal bactericidal concentration (MBC) to be 0.05 mg/ml. (¹¹ *Peloquin et al., 1997*)

INH is not recommended for use in the treatment of atypical mycobacterial infections, such as *Mycobacterium avium* complex (MAC), because INH has weak activity against MAC compared to other antimycobacterial agents. (²² *Toxnet*)

Resistance

Mycobacterium tuberculosis and other members of the M tuberculosis complex use several strategies to resist the action of antimicrobial agents. First, the mycobacterial cell is surrounded by a specialized, highly hydrophobic cell wall that results in decreased permeability to many compounds. Active drug efflux systems and degrading or inactivating enzymes and the genes that are associated with these functions, have been found in *M. tuberculosis*. (¹⁹ *Somoskovi et al., 2001*)

Resistance of *M. tuberculosis* to INH develops rapidly if it is used alone in the treatment of clinical infection, and may be due in some strains to loss of the gene for catalase production. Resistance is delayed or prevented by the combination of INH with other

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antimycobacterials where INH appears to be highly effective in preventing emergence of resistance to other antituberculous drugs. Resistance does not appear to be a problem when INH is used alone in prophylaxis, probably because the bacillary load is low. (⁹ *Martindale, 2009*; ¹⁹ *Somoskovi et al., 2001*)

There is a cross resistance between INH, rifampicin and ethambutol. However the simultaneous use of two of these drugs markedly delays the emergence of resistant mutants either agent. (⁸ *IPCS INCHEM, 1999*)

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2.5.4 Overview of Efficacy

2.5.4.1 Monitoring parameters

Patients with sputum smear-positive pulmonary TB should be monitored by sputum smear examination. For patients with sputum smear-negative pulmonary TB and extrapulmonary TB, clinical monitoring is the usual way of assessing the response to treatment. (²⁴ WHO, 2003)

New sputum smear-positive pulmonary TB patients (Category I)

Response to treatment should be monitored by sputum smear examination. In general, two sputum specimens should be collected for smear examination at each follow-up sputum check. Sputum smears should be performed at the end of the second month, during the fifth month and in the last month of the 6-month and 8-month treatment regimens. At the end of the second month of treatment, most patients will have a negative sputum smear and will then start the continuation phase of treatment. If a patient has a positive sputum smear at this time, this may indicate one of the following: (²⁴ WHO, 2003)

- most frequently, that the initial phase of therapy was poorly supervised and that patient adherence was poor;
- sometimes, that there is a slow rate of progress with sputum smear conversion, e.g. if a patient had extensive cavitation and a heavy initial bacillary load;
- rarely, that the patient may have drug-resistant TB that does not respond to first-line treatment.

Previously treated pulmonary sputum smear-positive patients (Category II)

Sputum smear examination is performed at the end of the initial phase of treatment (at the end of the third month), during the continuation phase of treatment (second month after starting continuation) and at the end of treatment. If the patient is sputum smear-positive at the end of the third month, the initial phase of treatment with 4 drugs is extended by another month and sputum smears are examined again at the end of the fourth month. If the patient still has positive smears at the end of the fourth month, sputum is sent to the

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laboratory for culture and sensitivity testing, where possible, and the patient then starts the continuation phase. If the culture and sensitivity results show resistance to 2 of the 3 drugs employed in the continuation phase, the patient should be referred to a specialized centre for consideration of treatment with reserve antituberculosis drugs. (²⁴ WHO, 2003)

New sputum smear-negative pulmonary TB patients (Category III)

Sputum smear-negative patients should be monitored clinically; body weight is a useful progress indicator. Sputum smears should be checked at the end of the second month in case of the following possibilities: disease progress due to non-adherence to treatment, or an error at the time of initial diagnosis (i.e. a true smear-positive patient misdiagnosed as smear-negative) plus drug resistance. (²⁴ WHO, 2003)

At the end of the treatment course for each patient with sputum smear-positive pulmonary TB, the treatment outcome is recorded as shown in Table 2. (²⁴ WHO, 2003)

Table 2. Recording treatment outcome in smear-positive TB patients

Cure	Patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion.
Treatment completed ^a	Patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure.
Treatment failure	Patient who is sputum smear-positive at 5 months or later during treatment. ^b
Died	Patient who dies for any reason during the course of treatment.
Default	Patient whose treatment was interrupted for two consecutive months or more.
Transfer out	Patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.

a Treatment success is defined as the sum of patients cured and those who have completed treatment.

b Also a patient who was initially smear-negative before starting treatment and became smear-positive after completing the initial phase of treatment.

2.5.4.2 Clinical Indications

INH is a component of all TB chemotherapeutic regimens currently recommended by WHO. (²⁴ WHO, 2003)

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INH alone is occasionally used to prevent: (²⁴ WHO, 2003)

- transmission to close contacts at high risk of disease;
- progression of infection to primary complex in recently infected, asymptomatic individuals;
- development of active TB in immunodeficient individuals.

2.5.4.2.1 Infections

Tuberculosis is caused primarily by *Mycobacterium tuberculosis* and occasionally by *M. bovis*. Infection results from inhalation of infected droplet nuclei. Primary infection is usually asymptomatic and in more than 95% of immune competent individuals is controlled by acquired (cell mediated) immunity. The immune response, however, is unable to eradicate the tubercle bacilli, and these bacilli may give rise to progressive primary infection (if disease occurs within 2 years of initial infection) or post-primary (reactivated) tuberculosis (if disease occurs years to decades after initial infection). Young children and immunocompromised patients are at increased risk of developing active disease. The most common manifestation of tuberculosis is pulmonary disease, although almost any organ may be affected. Patients usually present with cough, fever, night sweats, and weight loss. (⁹ Martindale, 2009)

During recent years the incidence of tuberculosis in many countries has increased in association with the increasing prevalence of HIV infection. WHO applies the term DOTS (Directly Observed Therapy – Short Course) to its tuberculosis control strategy, which includes standards for diagnosis, supervised therapy, ensuring secure drug supplies, and regular evaluation of the tuberculosis control programme. (⁹ Martindale, 2009)

2.5.4.2.2 Clinical Studies

Treatment of tuberculosis

The aims of treatment of TB are the following:

- to cure the patient of TB;
- to prevent death from active TB or its late effects;
- to prevent relapse of TB;

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- to decrease transmission of TB to others;
- to prevent the development of acquired resistance (²⁴ WHO, 2003)

There are three main properties of anti-TB drugs: bactericidal ability, sterilizing ability and the ability to prevent resistance. The anti-TB drugs possess these properties to different extents. INH and rifampicin are the most powerful bactericidal drugs, active against all populations of TB bacilli. Pyrazinamide and streptomycin are also bactericidal against certain populations of TB bacilli. Pyrazinamide is active in an acid environment against TB bacilli inside macrophages. Streptomycin is active against rapidly multiplying extracellular TB bacilli. Ethambutol and thioacetazone are bacteriostatic drugs used in association with more powerful bactericidal drugs to prevent the emergence of resistant bacilli. (²⁴ WHO, 2003)

INH, rifampicin, pyrazinamide and streptomycin are all as efficacious when given intermittently (2 or 3 times per week) as when given daily. Ethambutol is usually only given intermittently when also given with rifampicin. Thioacetazone is the only anti-TB drug not effective when given intermittently (2 or 3 times per week). (²⁴ WHO, 2003)

Treatment of tuberculosis involves more than one drug. This is based on two principles: preventing acquired drug resistance and enhancing efficacy. Tubercle bacilli undergo random chromosomal mutations that have made them resistant to every drug used to treat tuberculosis. Fortunately, these mutations are infrequent. Because they are unlinked (in terms of chromosomal location or function) and specific to a drug or drug class, spontaneous generation of an organism with multiresistance is extremely improbable. Acquired drug resistance for tuberculosis is almost always caused by inadequate treatment. This can include failure of the patient to take the prescribed drugs, failure of the physician to prescribe appropriately, failure of the healthcare system to ensure that drugs are available, or rarely - malabsorption of the drug(s) due to dysfunction of the digestive system or substandard bioavailability of the preparation. (⁶ Chan & Iseman, 2002)

New cases

Treatment of tuberculosis involves an initial (intensive) phase lasting 2 months and a continuation phase usually lasting 4-6 months. During the initial phase, consisting usually

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of 4 drugs, there is rapid killing of tubercle bacilli. Infectious patients become non-infectious within about 2 weeks. Symptoms improve. The vast majority of patients with sputum smear-positive TB become smear-negative within 2 months. In the continuation phase fewer drugs are necessary but for a longer time. The sterilizing effect of the drugs eliminates remaining bacilli and prevents subsequent relapse. (²⁴ WHO, 2003)

The American Thoracic Society (ATS), US Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) currently recommend several possible multiple-drug regimens for the treatment of culture-positive pulmonary tuberculosis. These regimens have a minimum duration of 6 months (26 weeks), and consist of an initial intensive phase (2 months) and a continuation phase (usually either 4 or 7 months). INH is considered a first-line antituberculosis agent for the treatment of all forms of tuberculosis caused by Mycobacterium tuberculosis known or presumed to be susceptible to the drug. (² AHFS, 2008)

Re-treatment cases

Previously treated TB patients include those patients treated as new cases for more than one month who are smear- or culture-positive (failure, relapse, return after default). Re-treatment cases have a higher likelihood of drug resistance, which may have been acquired through inadequate prior chemotherapy. Adherent patients who fail initial treatment are high risk of having multi-drug resistant (MDR) TB. (²⁴ WHO, 2003)

The standard re-treatment regimen consists of 5 drugs in the initial phase and 3 drugs in the continuation phase. The patient receives 3 drugs throughout the treatment; rifampicin (R), INH (H) and ethambutol (E). This standardized regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to INH and/or streptomycin. Under proper case management conditions, MDR-TB cases are those most at risk of failure in re-treatment regimen. (²⁴ WHO, 2003)

Treatment of Extrapulmonary Tuberculosis

Although most commonly affecting the lungs, tuberculosis can involve virtually any organ of the body. In countries with comprehensive diagnostic and reporting system,

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extrapulmonary tuberculosis accounts for 20-25% of reported cases, being relatively more frequent in children and persons with HIV infection. Of specific forms, lymphatic, pleural and bones or joint disease are the most common, while pericardial, meningeal and disseminated (miliary) forms are more likely to result in a fatal outcome. Most experts now agree that virtually all forms of extrapulmonary tuberculosis can be treated with regimens used for treatment of pulmonary tuberculosis. Adjunctive steroids may be useful in pericardial and meningeal tuberculosis. Surgery plays little role in the management of extrapulmonary tuberculosis. (²⁴ WHO, 2003)

HIV and Tuberculosis

In patients with HIV infection there is risk of drug interactions with antiretroviral agents, paradoxical reactions that may be interpreted as clinical worsening, and the potential for the development of acquired resistance to when treated with highly intermittent therapy. (⁵ CDC, 2003)

As HIV infection progresses, CD4 lymphocytes decline in number and function. The immune system is less able to prevent the growth and local spread of *M. tuberculosis*. Disseminated and extra-pulmonary disease is more common. The commonest forms are the following: lymphadenopathy, pleural effusion, pericardial disease, miliary disease, meningitis. (²⁴ WHO, 2003)

Generally, anti-TB chemotherapy is the same for HIV-infected as for non-HIV-infected TB patients, with the exception that thioacetazone is contraindicated in HIV infected. Deaths during treatment, partly due to TB itself and partly due to other HIV-related disease, are more frequent in HIV-infected patients, particularly in advance stages of immunodeficiency. Among TB patients who complete short-course chemotherapy, the recurrence rate is higher in HIV-positive than in HIV-negative TB patients. Post-treatment prophylaxis (for example with INH) can decrease the risk of TB recurrence in HIV-infected individuals, although it does not appear to prolong survival. (²⁴ WHO, 2003)

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DOTS

DOTS (directly-observed treatment, short-course) is an intermittent, supervised system of drug-intake by patient, which eliminates drug-default. The drugs used are the same as the ones used in short course chemotherapy i.e. INH, rifampicin, pyrazinamide, ethambutol and streptomycin. It has been described by WHO as "the most important public health breakthrough of the decade in terms of lives saved." The main advantages of DOTS are (i) Cure rates of upto 95%, (ii) Prevention of Multi-drug resistant TB emergence and (III) Improvement of longevity of AIDS patients by TB control. (¹⁰ *Murali & Sajjan, 2002*)

Currently, short-course chemotherapy comprising rifampicin, INH, pyrazinamide and ethambutol/streptomycin administered under directly observed settings for 6 months (initially all four drugs followed by the former two drugs), constitutes the cornerstone treatment for pulmonary tuberculosis. (²⁴ *WHO, 2003*)

Prophylaxis of tuberculosis

INH given for at least 6 months has been the standard therapy for latent tuberculosis infection for decades. The Joint Tuberculosis Committee of the British Thoracic Society and the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) recommend preventive therapy for a minimum of 6 months in patients at increased risk of developing TB, such as recent skin test converters, close contacts of known TB cases, or patients with positive skin tests with chronic medical conditions. The ATS & CDC guidelines recommend 12 months of INH for skin-test positive, HIV-positive patients. The effectiveness of INH prophylaxis in diverse populations has been demonstrated. There is a small advantage of 12 month over 6 month courses of INH preventive therapy. This small advantage of 12 over 6 month courses may not be worthwhile except for those at high risk of developing TB. The Joint Tuberculosis Committee recommends 6 months of INH preventive therapy for children exposed to M. tuberculosis, whereas the American Academy of Pediatrics recommends 9 months of therapy. (¹⁸ *Smieja et al., 2000*)

The primary risk of preventive therapy is the risk of INH-induced hepatitis. In the IUAT study, 1 person in 200 developed hepatitis, and 1 person in 7,000 died from INH-induced

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2.5.5 Overview of Safety

2.5.5.1 Adverse Events

Peripheral neuritis and hepatotoxicity are the most frequently observed adverse effects of INH.

Nervous System Effects

Peripheral neuritis, usually preceded by paresthesia of the feet and hands, is the most common adverse effect of INH and occurs most frequently in malnourished patients and those predisposed to neuritis (e.g., alcoholics, diabetics). Rarely, other adverse nervous system effects have also occurred including seizures, toxic encephalopathy, muscle twitching, ataxia, stupor, tinnitus, euphoria, memory impairment, separation of ideas and reality, loss of self-control, dizziness, and toxic psychosis. Neurotoxic effects may be prevented or relieved by the administration of 10–50 mg of pyridoxine hydrochloride daily during INH therapy, and pyridoxine should be administered in malnourished patients, pregnant women, and those predisposed to neuritis (e.g., HIV-infected individuals). In addition, optic neuritis and atrophy have been reported with INH. (² *AHFS, 2008*)

Hepatic Effects

Mild hepatic dysfunction, as evidenced by mild and transient increases in serum AST (SGOT), ALT (SGPT), and bilirubin concentrations, has occurred in approximately 10–20% of patients receiving INH, usually during the first 4–6 months of therapy. In most cases, enzyme concentrations return to pretreatment values despite continuation of INH, but progressive liver dysfunction, bilirubinuria, jaundice, and severe and sometimes fatal hepatitis have occurred rarely. The incidence of INH-associated hepatitis is lowest in patients younger than 20 years of age and greatest in daily users of alcohol and patients 35 years of age or older. The American Academy of Pediatrics (AAP) states that the incidence of hepatitis during INH therapy in otherwise healthy infants, children, and adolescents is rare and that routine determination of serum aminotransferase concentrations are not recommended. Progressive liver damage may occur in about 2% of

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patients older than 50 years of age who receive INH. However, data from one study suggest that hepatitis occurs in approximately 4.5% of patients older than 65 years of age who receive the drug. If symptoms of hepatitis or signs suggestive of hepatic damage occur during INH therapy, the drug should be discontinued promptly. (²AHFS, 2008)

Sensitivity Reactions

Hypersensitivity reactions, including fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy, vasculitis, and, rarely, hypotension, have occurred rarely with INH, usually 3–7 weeks following initiation of therapy. At the first sign of a hypersensitivity reaction, all drugs should be discontinued. If INH is reinstated, the drug should be restarted in small and gradually increasing doses only after symptoms have cleared. If there is any indication of recurrence of hypersensitivity, INH should be discontinued immediately. (²AHFS, 2008)

Hematologic Effects

Adverse hematologic effects, including agranulocytosis, eosinophilia, thrombocytopenia, methemoglobinemia, and hemolytic, sideroblastic or aplastic anemia, have occurred in patients receiving INH. (²AHFS, 2008)

Other Adverse Effects

Other reported adverse effects of INH include nausea, vomiting, epigastric distress, dryness of the mouth, pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and urinary retention and gynecomastia in males. A systemic lupus erythematosus-like syndrome and a rheumatic syndrome with arthralgia have also occurred. IM administration of INH has caused irritation at the site of injection. (²AHFS, 2008)

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2.5.5.2 Overdose

Manifestations

Overdosage of INH causes nausea, vomiting, dizziness, slurred speech, blurred vision, and visual hallucinations (including bright colors and strange designs). Symptoms of overdosage usually occur within 30 minutes to 3 hours following ingestion of the drug. After marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to coma, severe intractable seizures, metabolic acidosis, acetonuria, and hyperglycemia have occurred. If untreated or treated inadequately, INH overdosage may be fatal. INH-induced seizures are thought to be associated with decreased γ -aminobutyric acid (GABA) concentrations in the CNS, possibly resulting from inhibition by INH of brain pyridoxal-5-phosphate activity. (² *AHFS, 2008*)

Doses of 35 to 40 mg/kg have resulted in seizures. Doses of 80 to 150 mg/kg will produce seizures and may cause death. Acute ingestion of 2 to 3 grams in an adult is potentially toxic while 10 to 15 grams is frequently associated with death if untreated. (²² *Toxnet*)

Treatment

In the management of INH overdosage, an airway should be secured and adequate respiratory exchange established immediately. Seizures may be controlled with IV administration of diazepam or short-acting barbiturates and a dosage of pyridoxine hydrochloride equal to the amount of INH ingested. Generally, 1–4 g of pyridoxine hydrochloride is given IV followed by 1 g IM every 30 minutes until the entire dose has been given. If seizures are controlled and overdosage is recent (within 2–3 hours), the stomach should be emptied by gastric lavage. Blood gases, serum electrolytes, glucose, and BUN determinations should be performed. Blood should be typed and cross-matched in case hemodialysis is required. IV sodium bicarbonate should be administered to control metabolic acidosis and repeated as needed; dosage should be adjusted on the basis of laboratory test results. Pyridoxine has also had a beneficial effect in correcting acidosis in some patients, possibly by controlling seizures and resulting lactic acidosis. Pyridoxine has been effective in treating INH-induced seizures as well as other mental status changes associated with INH overdosage. In several patients who remained comatose following

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initial treatment of seizures with diazepam and pyridoxine, administration of an additional 3- to 5-g dose of pyridoxine hydrochloride after 36–42 hours of coma resulted in complete awakening within 30 minutes. The fact that administration of high doses of pyridoxine can result in adverse neurologic effects should be considered whenever the drug is used in the treatment of INH-induced seizures and/or coma. (² *AHFS, 2008*)

Forced osmotic diuresis should be initiated as soon as possible following INH overdose to increase renal clearance of the drug and should be continued several hours after clinical improvement to ensure complete clearance of the drug and prevent relapse. Fluid intake and output should be monitored. In severe cases, hemodialysis or, if hemodialysis is not available, peritoneal dialysis should be used in conjunction with forced diuresis. In addition, measures should be taken to protect against hypoxia, hypotension, and aspiration pneumonitis. (² *AHFS, 2008*)

2.5.5.3 Interactions

INH inhibits the metabolism of several drugs, resulting in clinically significant interactions in some patients. Clinical trials and case reports have documented that INH can cause increased phenytoin and carbamazepine serum concentrations and toxicity. In relatively high doses, INH can also cause increased effect of theophylline and warfarin. INH inhibits metabolism of selected benzodiazepines and vitamin D. Inhibition of monoamine oxidase and histaminase by INH can cause significant drug-food interactions. Food greatly decreases INH bioavailability. Although probably best recognized as an inhibitor of drug metabolism, INH has a biphasic effect of inhibition-induction on one cytochrome P450 isozyme, CYP2E1, which partially explains the interaction with acetaminophen and increased risk of hepatotoxicity. The major drug-food interactions of INH are summarized in tables 3 and 4. (¹⁶ *Self et al., 1999*)

Table 3. Examples of INH Drug Interactions

<u>Drugs</u>	<u>Comments</u>
Acetaminophen	Cautious use of repeated dosing during INH therapy; advise patients to promptly report symptoms associated with hepatitis.
Antacids	Decreased INH absorption; primarily shown with aluminum hydroxide; give INH at least 1 hour before antacids

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Benzodiazepines	Monitor for symptoms of increased benzodiazepine effect; affects only benzodiazepines metabolized by oxidation: if concurrent rifampicin therapy, anticipate decreased effect of benzodiazepine.
Carbamazepine	Monitor patient for symptoms of toxicity; monitor serum carbamazepine concentrations; anticipate need to adjust dose.
Isoflurane	Increase in serum fluoride ion is possible; clinical relevance unlikely.
Phenytoin	Monitor patient for symptoms of toxicity; monitor serum phenytoin concentrations; anticipate need to adjust dose; if concomitant rifampicin therapy, phenytoin concentrations will probably decrease.
Theophylline	Monitor serum theophylline concentrations; increase in serum levels most likely if INH dose ≥ 10 mg/kg/day; if concomitant rifampicin therapy, theophylline concentrations will probably decrease.
Vitamin D	INH alone may decrease serum calcium, phosphate and $1\alpha,25$ dihydroxyvitamin D; concurrent rifampicin attenuates the effect of INH on vitamin D; INH-rifampicin may mask primary hyperparathyroidism
Warfarin	Monitor INR; increase in INR most likely with INH dose > 300 mg/day

Table 4. INH food interactions

Regular meals	Delay and decrease absorption of INH; take INH on an empty stomach or at least 1.5 hours before a meal; occurs with any food but especially carbohydrates
Foods high in tyramine	Monitor patients for flushing, palpitations, headache, itching, nausea and vomiting; avoid foods high in tyramine, such as Swiss, Cheshire, Gruyere cheeses or red wine
Foods high in histamine	Monitor patients for flushing, palpitations, headache, itching, nausea and vomiting; avoid foods with high histamine content, such as tuna

Other Interactions

Anti-tubercular Drugs:

There is some evidence that adverse nervous system effects of INH, cycloserine, and ethionamide may be additive; therefore, INH should be used with caution in patients receiving cycloserine or ethionamide. Aminosalicic acid appears to reduce the rate of

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acetylation of INH; the effect is usually not clinically important. INH inhibits multiplication of bacille Calmette-Guérin (BCG); therefore BCG vaccine may not be effective if administered during therapy with the drug. (² *AHFS, 2008*)

A statistically significant increase in the incidence of hepatotoxicity was found with coadministration of INH and rifampicin compared with the incidence associated with either drug by itself. (⁷ *Drugdex, 2006*)

Disulfiram

Coordination difficulties and psychotic episodes have occurred in patients receiving INH and disulfiram concurrently, probably as a result of alterations in dopamine metabolism; concurrent administration of the drugs should be avoided. (² *AHFS, 2008*)

Itraconazole and Ketoconazole

Concomitant administration of INH with itraconazole may result in significant decreases in itraconazole serum concentrations and therapeutic failure. Coadministration is not recommended. (⁷ *Drugdex, 2006*)

INH can inhibit certain cytochrome P-450 enzymes, including the ones responsible for ketoconazole metabolism. Consequently, ketoconazole metabolism can be reduced and dosage adjustments may be necessary. (⁷ *Drugdex, 2006*)

Levodopa

Concomitant INH and levodopa therapy has resulted in agitation, flushing, palpitations, severe non-parkinsonian tremor, and elevated blood pressure. INH acts as a monoamine oxidase inhibitor and may cause excess catecholamine stimulation when combined with the dopamine precursor levodopa. (⁷ *Drugdex, 2006*)

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Anti-virals

The clearance of INH was approximately doubled when zalcitabine was given to HIV-positive patients. In addition, care is needed since stavudine and zalcitabine may also cause peripheral neuropathy; use of INH with stavudine has been reported to increase its incidence. (⁹ *Martindale, 2009*)

2.5.5.4 Precautions

INH should be used with caution in patients with convulsive disorders, a history of psychosis, or hepatic or renal impairment. Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine, usually in a dose of 10 mg daily, although up to 50 mg daily may be used. If symptoms of hepatitis develop, such as malaise, fatigue, anorexia, and nausea, INH should be stopped pending evaluation. (⁹ *Martindale, 2009*)

Liver function should be checked before treatment with INH and special care should be taken in alcoholic patients or those with pre-existing liver disease. Regular monitoring of liver function is recommended in patients with pre-existing liver disease, and the British Thoracic Society has recommended that INH treatment be suspended if serum aminotransferase concentrations are elevated to more than 5 times the normal upper limit or the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first INH, then rifampicin, and then pyrazinamide. Careful monitoring should be considered for black and Hispanic women, in whom there may be an increased risk of fatal hepatitis. (⁹ *Martindale, 2009*)

When visual symptoms occur during INH treatment periodic eye examinations have been suggested. (⁹ *Martindale, 2009*)

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Pregnancy

INH is considered to be relatively safe for both the mother and the fetus for treating active tuberculosis infection in pregnancy. Although a clear causal relationship has not been established, pulmonary tuberculosis infection itself has been associated with a significantly higher frequency of miscarriage. There are also case reports of infants with congenital tuberculosis, and drug-resistant disease may present an increased risk to the fetus. The current recommendation for the treatment of latent tuberculosis infection is INH, either daily or twice a week. For those patients at an increased risk for progression of latent tuberculosis infection to fulminant disease, especially HIV-positive women, initiation of therapy should not be delayed based on pregnancy alone, including the first trimester. Careful clinical and laboratory monitoring for hepatitis is recommended. Pyridoxine supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding. (⁷ *Drugdex, 2006*)

Lactation

INH is considered compatible with breastfeeding by the American Academy of Pediatrics. Because INH is distributed into breast-milk, infants who are also receiving INH therapy should be monitored for excessive accumulation of INH. The World Health Organization recommends monitoring the infant for jaundice; if significant jaundice develops, stop or change drug treatment. Pyridoxine supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding. (⁷ *Drugdex, 2006*)

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2.5.6 Benefits and Risks Conclusions

2.5.6.1 Benefits-risk Analysis

Pharmacokinetics

INH is readily absorbed from the gastrointestinal tract. Peak concentrations appear in blood 1 to 2 hours after an oral fasting dose of 300 mg. The rate and extent of absorption of INH is reduced by food. INH undergoes appreciable presystemic (first pass) metabolism in the wall of the small intestine and liver. INH does not accumulate appreciably with multiple daily doses, hence samples obtained as early as the first day of therapy will reflect steady state values.

INH is not considered to be bound appreciably to plasma proteins and distributes into all body tissues and fluids, including the CSF. CSF concentrations of the drug are reported to be 90–100% of concurrent plasma concentrations. INH readily crosses the placenta and is distributed into milk in concentrations approximately equal to maternal plasma concentrations. INH is distributed in total water with a mean apparent distribution volume of 0.6 to 0.75 L/kg.

INH is acetylated to acetylisoniazid by N-acetyltransferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinuric acid) and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised INH is conjugated to hydrazones. The metabolites of INH have no tuberculostatic activity. The rate of acetylation of INH and monoacetylhydrazine is genetically determined. Two groups of people can be distinguished on the basis of their capacity to acetylate INH: slow acetylators and fast acetylators. Metabolism of INH varies widely in different individuals, with half-lives of 80 ± 30 minutes for rapid acetylators and 180 ± 70 minutes for slow acetylators. Despite these differences, both acetylator types have roughly equivalent responses to treatment in clinical trials except when the dosing interval is extended to once weekly. In that seldom used regimen, slow acetylators had better responses.

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In adults with normal renal function, approximately 75–96% of a 5-mg/kg oral dose of INH is excreted in urine within 24 hours as unchanged drug and metabolites. 93% of the INH excreted in the urine may occur as the acetylated form in fast acetylators and 63% in slow acetylators.

The pharmacokinetics of INH is not greatly influenced by other antitubercular drugs such as rifampicin, pyrazinamide and ethambutol used in combination with INH.

The pharmacokinetics of INH in the elderly is similar to younger adults; however, the risk of hepatotoxicity seems to increase with age. Children as a group eliminate INH faster than adults with younger children eliminating INH faster than the older ones.

In patients with renal impairment there is no need to reduce INH dose except in cases where creatinine clearance is less than 10 mg/ml. However, in patients with acute or chronic liver disease INH dosage may require adjustment to avoid adverse effects of the drug.

Pharmacodynamics

INH is a hydrazide derivative. It is bactericidal in vitro and in vivo against actively dividing tubercle bacilli; it is less active against non-dividing tubercle bacilli being only bacteriostatic. INH is a prodrug and is activated by mycobacterial catalase peroxidase enzyme to generate a reactive isonicotinoyl radical that forms adducts with cellular pyridine nucleotide coenzymes, NAD^+ and $NADP^+$. The adducts thus formed are potential inhibitors of lipid and nucleic acid biosynthesis. Evidence supports the concept that INH blocks the synthesis of cell-wall mycolic acids, the major components of the envelope of *M. tuberculosis*. Because mycolic acids are unique to mycobacteria, INH selectively acts only against mycobacteria.

Resistance of *M. tuberculosis* to INH develops rapidly if it is used alone in the treatment of clinical infection and may be due in some strains to loss of the gene for catalase production. Resistance is delayed or prevented by the combination of INH with other antimycobacterials where INH appears to be highly effective in preventing emergence of

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resistance to other antituberculous drugs. Resistance does not appear to be a problem when INH is used alone in prophylaxis, probably because the bacillary load is low.

Efficacy and Safety

INH was introduced in 1952 and has been the mainstay of treatment of tuberculosis for more than 50 years. During this period, a very large number of patients have used the drug and it has been observed that the drug is well tolerated at the recommended doses.

INH is a component of all TB chemotherapeutic regimens currently recommended by WHO. INH alone is occasionally used to prevent:

- transmission to close contacts at high risk of disease;
- progression of infection to primary complex in recently infected, asymptomatic individuals;
- development of active TB in immunodeficient individuals.

INH is used with great success both in the initial phase and in the continuation phase of treatment of new cases of TB, re-treatment of TB, treatment of extra-pulmonary TB, treatment of TB associated with HIV and in DOTS. INH is also used alone for at least 6 months as standard therapy for latent tuberculosis.

INH is generally well tolerated. Peripheral neuritis and hepatotoxicity are the most frequently observed adverse effects of INH. Peripheral neuritis occurs most frequently in malnourished patients and those predisposed to neuritis (e.g., alcoholics, diabetics). Neurotoxic effects may be prevented or relieved by the administration of 10–50 mg of pyridoxine hydrochloride daily during INH therapy. The incidence of INH-associated hepatitis is lowest in patients younger than 20 years of age and greatest in daily users of alcohol and patients 35 years of age or older.

2.5.6.2 Conclusions

INH is bactericidal in vitro and in vivo against actively dividing tubercle bacilli. INH blocks the synthesis of cell-wall mycolic acids, the major components of the envelope of *M tuberculosis*.

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INH is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than 1 hour in fast acetylators to more than 3 hours in slow acetylators. It is largely excreted in the urine within 24 hours, mostly as inactive metabolites. Combination with other anti-tubercular drugs does not appear to affect the pharmacokinetics of INH.

INH is the mainstay in the primary treatment of pulmonary and extra-pulmonary tuberculosis being part of initial and continuation phases of all regimen recommended by WHO. In addition, INH is recommended in re-treatment of TB, treatment of TB associated with HIV and in DOTS. INH is also recommended for use alone in the treatment of latent tuberculosis. INH is well tolerated. Peripheral neuritis and hepatotoxicity are the most frequently observed adverse effects of INH.

Few agents have been studied as extensively as INH. In spite of its use for more than 50 years, INH continues to be the cornerstone of all primary antituberculosis regimens and remains the only agent recommended for tuberculosis chemoprophylaxis. INH is most valued for its powerful bactericidal effect against the metabolically active organisms most commonly encountered in the sputum of adults with cavitating pulmonary tuberculosis and is the most valuable agent for preventing the development of resistance in companion agents.

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Company Name	
Registration file Drug Name Active substance:	Company Address
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