International Journal of PharmaO2
Journal Home Page: http://www.ijpo.in/
(IJPO: A Peer-reviewed Bi-monthly online journal)

Anti-Tubercular Agents: Overview

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Abstract

During the last few years, the pharmacy profession has expand significantly in terms of professional services delivery and now has been recognized as an important profession in the multidisciplinary provision of health care. The main objectives of tuberculosis therapy are to cure the patients and to minimize the possibility of transmission of the bacillus to healthy subjects. Adverse effects of antituberculosis drugs or drug interactions (among antituberculosis drugs or between antituberculosis drugs and other drugs) can make it necessary to modify or discontinue treatment. We describe the general mechanism of action, absorption, metabolization, and excretion of the drugs used to treat multidrug resistant tuberculosis (aminoglycosides, fluoroquinolones, cycloserine/terizidone, ethionamide, capreomycin, and para-aminosalicylic acid). We describe adverse drug reactions and interactions (with other drugs, food, and antacids), as well as the most appropriate approach to special situations, such as pregnancy, breastfeeding, liver failure, and kidney failure.

Keywords: Bactericidal, Bacteriostatic, Neuritis, Tuberculosis.

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Received on: 16/06/2020; Accepted on: 20/06/2020.

Introduction

Robert Koch in 1882, discovered tubercle bacillus thus the disease was referred as tuberculosis. It's a systematic disease commonly involves in respiratory system but affect other organs.

Tuberculosis is a disease caused by Mycobacterium tuberculae, a bacteria that is passed between people through the air.The disease can be cured with proper drug therapy, but because the bacteria may become resistant to any single drug combinations of antituberculosis drugs are used

to treat tuberculosis (TB) are normally require d for effective treatment. Atthe start of the 20th Century, tuberculosis was the most common c ause of death in the United States, but was lare glyeliminated with better living conditions. It is most common in areas of crowding and poor v entilation, suich as crowdedurban areas and pri sons. In some areas, the AIDS epidemic has be en accompanied by an increase in the prevalenc e of tuberculosis (Goodman and Gilman, 2000).

Some antituberculosis drugs also are used to tre at or prevent other infections such as *Mycobacterium avium* complex (MAC).

In Brazil, tuberculosis treatment regimens have been standardized by the Brazilian National Ministry of Health since 1979. According to the latest technical norms, published in October of 2009, the treatment recommended for all new cases of pulmonary and extrapulmonary tuberculosis, as well as for all cases of recurrence and retreatment due to noncompliance, is the use of a fixed-dose, single-tablet combination of rifampin, isoniazid, pyrazinamide, and ethambutol for two months and, in the second phase, a combination of isoniazid and rifampin for another four months (2RHZE/4RH regimen). In cases of meningoencephalitis due to tuberculosis, the same initial regimen, with the addition of a corticosteroid in the first month of treatment, is recommended. The second phase extends for seven months. A number of treatments have been proposed for cases of intolerance to one of the first-line drugs and for other clinical situations, such as liver disease. (Goodman & Gilman's, 2000). Patients with bacilli that are resistant to isoniazid and rifampin, patients with bacilli that are resistant to isoniazid, rifampin, and another first-line drug, and patients in whom the basic regimen fails constitute a group of patients classified as having multidrug resistant tuberculosis. For cases such as these, a combination regimen of streptomycin, ethambutol, terizidone, pyrazinamide, and one quinolone (levofloxacin or ofloxacin) has been proposed. If streptomycin cannot be used, it should be replaced with amikacin. Patients with extensively drug-resistant tuberculosis should be referred to a tertiary referral center, and individualized salvage drug regimens (which include capreomycin, moxifloxacin, para amino salicylic acid, and ethionamide) should be used (Marcos Abdo Arbex, Marília de Castro Lima Varella, *et al*, 2010) (Simon Tiberi, Anna Scardigli, 2017).

In this review article, we describe the principle characteristics of each of the drugs that constitute the alternative regimen for tuberculosis treatment proposed by the Brazilian National Ministry of Health and the

Brazilian Thoracic Association, as well as the relevant aspects of the pharmacokinetics of the drugs in order to understand the mechanisms of interaction and possible adverse effects (Patrick J. Brennan, Douglas B. Young, 2008) (Marcos Abdo Arbex, Marília de Castro Lima Varella, 2010).

Definition of Tuberculosis:

Tuberculosis is a chronic infectious disease which may caused by *Mycobacterium Tuberculosis* is called as tuberculosis (Goodman & Gilman's, 2000).

Tuberculosis Consists: (K.D. Tripathi, 2008)

1. Primary Pulmonary Tuberculosis (PPT):
   - With primary tuberculosis the source of organism is exogeneous.
   - It occurs in individual who may loss their sensitivity for autoimmune system of body to *tubercule bacillus* & also may develops primary tuberculosis more than once.
2. Secondary Pulmonary Tuberculosis (SPT):
   - It is also called as reactive tuberculosis.
   - It may follow shortly after primary pulmonary tuberculosis in which resistance of the body is decrease.
   - It is an exogenous re-infection it is manly found in the apex of one or both the upper lobes of lungs.
3. Milliary Tuberculosis (MT):
   - It is an extra- pulmonary form which results from progressive primary tuberculosis as well as secondary tuberculosis.
   - This is a lymphohaematogeneous disease which spread in later stages into systemic organ or isolated organ as liver ,kidney ,brain, pulmonary artery ,lymph nodes and bone cells etc.

Definition of Anti-Tuberculosis: (K.D. Tripathi, 2008)

Anti-tuberculosis may be defined as these are the pharmacological agent which when administer they use in treatment of tuberculosis (T.B)

Classification of Anti-Tubercular Drugs:

Classification of Anti-tubercular drug is based on their efficiency of low toxicity (safety). The agents are classified into two groups:

A. First Line Agents (S.R. Kale & R.R. Kale, 2008)

1. Bacteriostatic (These are the agent which stop the growth of bacteria or micro-organisms). Eg: Etambutol (E), Paraminosalicylic (PAS), Thiacetazone(T)

2. Bactericidal: (These are the agent which are use to kill the bacteria or micro-organisms). Eg: Isoniazide(INH), Rifampicin(R), Streptomycin(S)

B. Second Line Agents (S.R. Kale & R.R. Kale, 2008)

1. Bacteriostatic: Eg: Etionamide(Eth), Cycloserin(C)

2. Bactericidal: Eg: Kenamycin(k), Cycloserin(C)

First Line Agents: (S.R. Kale & R.R. Kale, 2008)

F= Field defects causing drug i.e. Ethambutol (E).

I= Isoniazid (I).

R= Rifampicin (R)

S=Streptomycin (S)

T= Twice a day given drugs i.e. Pyrazinamide.

(All the first line drugs are given once a day).

In general the FIRST line drugs used to treat-drug sensitivity T.B. are better tolerated than the SECOND line medication for drug resistant T.B.

Eg: Isoniazide, Rifampicin, Pyrazinamide, Ethambutol, Streptomycin.

Second Line Agents These drugs have either low anti-tubercular efficacy or high toxicity or both used in special circumstances only.

Eg: Ethionamide, Cycloserin, Amikacin, Aminosalicylic acid.

Mechanism of Action

(S.R. Kale & R.R. Kale, 2008)

– Interference with initiation complex of peptide formation.

– Misreading of code of m-RNA.

– Incorporation of incorrect Amino acid into the peptide chain.

– Resulting on non-functional or toxic protein.

– Inhibition of translocation.

– Break up of polysome into non functional monosomes.

– The activity occurs simultaneously & overall effect is the lethal for the cell.

Identification Test for Tuberculosis

Tuberculin or Mantoux Test (A.K. Gupta, 2016)

a. This Test is performed to find out whether any particular person had any previous tuberculosis infections or not.

b. Sufficient quantity of tuberculin solution (5 tuberculin units) is administered intradermaly into the skin of the left forearm.

c. The site of the Injection is examined after 72 hrs i.e. Three Days.

d. This Test is considered positive if there is swelling of at least 6-10mm in diameter at the site of Injections.

e. The Redness of the skin is no considerations.

f. Reactions less than 6 mm in diameter are considered negative and BCG Vaccination is therefore administered.

g. Preliminary tuberculin testing for new- born infants is unnecessary.

First Line Drug

Isoniazid (Inh) (Marcos Abdo Arbex, Marília de Castro Lima Varella, 2010).

Isoniazid is one of the most important drug in the used in treatment of tuberculosis. It has been used since 1952. The structure of isoniazid is simple. It comprises a pyridine ring and a hydrazine group. The minimum inhibotry concentration of isoniazid for mycobacterium tuberculosis is 0.02-0.20.

Mechanism of Action of Isoniazid (Goodman and Gilman, 2000).

a. Isonizid is a prodrug and must be ACTIVATED BY THE *Mycobacterium Tuberculosis* catalase- peroxidase enzyme KatG;

b. The activation of isoniazid produces oxygen derived from free radicals (superoxide, Hydrogen peroxide)

c. Organic free radicals that inhibit the formation of MYCOIC ACID of the bacterial cell wall.

d. Which causing DNA damage & subsequently the death of the bacillus.

e. The most common mechanism of resistance to isoniazid consists of K at G Mutation.

f. Which is decreases the activity of isoniazid & prevent the PRODRUG from being converted into its active metabolites.

Pharmacokinetics of Isoniazid

- Isoniazid is completely absorbed orally& penetrates all the body tissues tubercular cavities, placenta mengis.
- Isoniazide is metabolized in liverthrough bacetylation by N-acetyltransferase which produces acetylisoniazid & isonicotinic acid.
- It is extensively metabolized in liver most (important pathway being acetylation.
- Isoniazid is excreted by kidney in the form of urine.
- Fast acetylators
- (30-40%of Indians) t1/2 of INH 1 Hrs.
- Slow acetylators, (60-70% of Indians) t1/2 Of INH 3 hrs.
- The proportion of the fast & slow acetylators different in different part of the world.
- However acetylator s status do not matter.
- If INH taken orally or daily but biweekly regimers are less effective in fast acetylator.
- INH induced peripheral neuritis appears to be more common in slow *acetylatiors.*

Preparation of Isoniazid (S.R. Kale & R.R. Kale, 2008)

- Isoniazid elixir (syrup).
- Isoniazid injections.
- Isoniazid & rifampicin tablets
- Isoniazid & Ethambutol tablet

Trade Name of Isoniazid

- Ionex
- Rimpazid

– Isocadipas
– Cadizide

Therapeutic Uses of Isoniazid (Goodman & Gilman's, 2000).

– Isoniazid use in treatment of pulmonary tuberculosis.
– Isoniazid also use in treatment of Extra-pulmonary Lesions including menengeal & Genito urinary infections.
– As isoniazid develops registance within a few weeks.
– It gives in combination with ethambutol or Rifampicin.

Contraindications: (Goodman & Gilman's, 2000).

– It should be contraindicated in following conditions .
– Diabetes is not under control
– Habit of drinking too much alcohol
– Acute Liver Failure
– Poor Nutrition
– Gout
– several Renal Impairment
– Peripheral Neuropathy

Preperation of Antitubercular Drugs (K.D. Tripathi, 2008; S.R. Kale & R.R. Kale, 2008)

-Isoniazid…….100 -300 mg Tablets
-isoniazid……100mg/5ml Solution
-Isoniazid……...10mg/ml Oral Suspension
-Pyrazinamide …....100mg/ml Oral Solutions
-Cycloserine……..250mg Capsule
-Kenamycin……..0.5-0.75gm/ml Injections
-Rifampicin…….150,300,450mg Capsule
-Rifampicin……300,450,600mg Tablet

Trade Names /Brand Names:

-Isonex
-Isocadipas
-Cadizide
-Rimpazid
-Idipas

Mode of Transmission (A.K. Gupta, 2016)

-It is spread by droplet infection
-By direct contact with the patient
-By consuming milk derived from a cow suffering from Tuberculosis
-By handling sputum and other discharges of the tuberculosis patients
-By consuming articles of food and drinks contaminated tubercule bacilli.
-When the droplets are expelled by tubercular patient through coughing, sneezing, talking and are inhaled by then healthy person.

Signs and Symptoms of Tuberculosis

- Pyrexia (Normally rise in body temperature in evening)
- Fatigue, malaise and loss of body weight.
- Anorexia (Loss of appetite), Night sweat
- Slight palpitation and rapid pulse.
- Chronic cough and hoarseness of throat.

- The breath has peculiar odour and sputum copoious .
- In women suffering from tuberculosis the Mensturation may become absent or scanty.
- Pulmonary artery in tubercle region breaks, which results into massive haemorrhage.

Treatment of Tuberculosis (S.R. Kale & R.R. Kale, 2008)

– Drug resistance is the main difficulty in management of tuberculosis hence to avoid it.

– The Antitubercular Agents are always use in combinations.

– The various Therapy advise as follows

1) **Optimum Antitubercular Therapy :**

In this combination three regiments or Drugs is advised

a) INH +R + S OR E……All Drug given daily for Two Months and followed by;

INH +R……..For Seven Months.

b) INH + R + S + Z…….. Daily for Two Months followed by;

INH + R Twice a Week or Daily Followed by;

INH + S + Z……..Twice a Week for Four Months.

2) **Two Drug Therapy:** This includes Daily a supervise administer of INH + S + E / PAS / T For Two Months Followed by Daily self administration of INH + E/ PAS + T. For 16 Months. In some cases it will be administer up to 22 months.

3) **Intermittent, Supervised Treatment:** It includes administration of INH + S or INH + E Twice a Week for 18 Months.

4) **Low Cost Regime or Drugs:** This includes administrations of; INH + R for Two Months Followed by INH + T For 8 Months.

Conclusion

The treatment of tuberculosis can cause adverse reactions. The management of situations that are more severe is generally the responsibility of referral centers and experienced professionals with knowledge of the therapeutic alternatives available. Accurate diagnoses and knowledge of the pharmacological properties of the drugs involved allow professionals.

Acknowledgement

The authors thankful to SMBT Sevabhavi trust for valuable support.

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