CHAPTER III

TREATMENT

Currently, there are nine (9) antituberculosis drugs available in the Philippine market. They are classified into first-line and second-line drugs.

Five drugs are considered first-line agents because of their potency, and level of efficacy with acceptable degree of toxicity.[10,11,12] They are also easily administered. The effectiveness of a drug to prevent emergence of resistance depends upon the extent to which they can continuously inhibit bacillary growth.[10]

The treatment regimen varies from doctor to doctor since there is no standard therapy. The usual practice is triple therapy consisting of INH, rifampin and pyrazinamide for the first 2 months, then rifampin and INH, on the succeeding 4 months or for far-advanced cases, quadruple therapy is instituted for the first 2-3 months. These consist of INH, rifampin, pyrazinamide and ethambutol or streptomycin. Pyrazinamide is removed at the end of the 3rd month.

Knowledge of pharmacokinetics and pharmacodynamics is essential to a practicing physician.

I. First-line anti-tuberculosis drugs

A. Isoniazid (INH)

Isoniazid is still the most widely used of all anti-TB drugs. It is bacteriostatic for "resting" bacilli but is bactericidal for rapidly dividing microorganisms.[8] Its exact mechanism of action is not known however, it is believed to inhibit the biosynthesis of mycolic acids which is an important constituent of the mycobacterial cell wall.[10] It is very effective, relatively nontoxic, inexpensive and can be administered once daily.

The drug is metabolized by acetylation in the liver at a rate that is genetically determined as either rapid or slow.[13,14]

It is readily absorbed orally or parenterally. Peak plasma concentration of 3 to 5 ug/ml develops 1 to 2 hours after oral intake. It penetrates well into body fluids and cells and caseous materials.[14]

Hepatitis is the major side effect of isoniazid. A study conducted by US Public Health Service showed that the rate of hepatitis increased proportionately with increasing age.[8,13] Stead's study in Arkansas indicated the risk of isoniazid-hepatitis increased to 5% in persons 65 years or older.[13] This however is not common to Filipinos.

Because isoniazid interferes with the metabolism of pyridoxine, reversible peripheral neuropathy is associated

with isoniazid administration. This is uncommon at a dose of 5 mg/kg. In patients with greater risk of developing isoniazid-associated neuropathy, pyridoxine at 100 mg/day is supplemented.[13] Such patients include diabetics, uremics, alcoholics and the poorly nourished.[13,10]

Isoniazid increases the serum concentration of phenytoin, disulfiram, carbamazepine, anti-coagulants, benzodiazepines and vitamin D.

Bacterial Resistance[10]:

When tubercle bacilli are grown in vitro in increasing concentrations of isoniazid, mutants are readily selected that are resistant to the drug, even when the drug is present in enormous concentrations. It is believed that the mechanism of resistance is related to failure of the drug to penetrate or to be taken up by the microorganisms. About one in 10^6 tubercle bacilli will be genetically resistant to the drug. Tuberculous cavities may contain as many as 10^7 to 10^9 microorganisms hence, treatment with INH alone results in the selection of these resistant bacteria.

B. Rifampin (RIF)

Rifampin is a semisynthetic derivative of rifamycin, a macrocyclic antibiotic produced by Streptomyces mediterraneae. It inhibits the growth of most gram positive and many gram negative microorganisms. In concentrations

of 0.005 to 0.2 ug/ml, it inhibits the growth of M. tuberculosis in vitro.[10] It increases the in vitro activity of streptomycin and isoniazid against M.tuberculosis.

Peak plasma concentration in 2-4 hours after ingestion is approximately 7 ug/ml. It is easily administered and relatively non-toxic ; however, it is expensive.[13]

It penetrates well into tissues especially in the presence of inflammation. The half-life varies from 1.5 to 5 hours and is increased in the presence of hepatic dysfunction; it maybe decreased in patients receiving INH concurrently who are slow inactivators of INH.[10]

It is distributed through out the body and is present in effective concentrations in many organs and body fluids. Patients are therefore advised that the drug may impart an orange color to the urine, feces, saliva, sputum, tears and sweat.[8]

Hepatitis from rifampin rarely occurs in patients with normal hepatic function. The incidence of hepatic problem increases when rifampin is given alone or with INH in patients with chronic liver disease, alcoholics and the aged.[8,14,10]

Rifampin should never be used alone in the treatment of tuberculosis due to the rapidity of developing resistant strains to it.

Bacterial Resistance:[10]

Mycobacteria may develop resistance to rifampin rapidly in vitro as a one-step process, and one of every 10^7 to 10^8 tubercle bacilli is resistant to the drug. This also appears to be the case in vivo and the drug must not be used alone in the treatment of tuberculosis.

C. Pyrazinamide (PZA)

It is a uniquely active drug against tubercle bacilli in an acid environment. The drug is active against organisms in macrophages but lacks the ability to suppress all bacilli continuously.[10] It is an important sterilizing drug but relatively ineffective in preventing the emergence of resistance. Peak serum concentrations of 30 to 50 ug/ml exceed the minimum inhibitory concentration for M.tuberculosis and are achieved 2 hours after oral intake.[13] Half-life is 9 to 10 hours. It has good tissue penetration.

Liver injury is the outstanding side effect, usually dose-related. It also inhibits excretion of urate and acute episodes of gout have occurred in some patients.[8]

D. Ethambutol (EM)

Ethambutol is a water soluble and heat stable compound. In standard dose of 15 mg/kg, it is bacteriostatic against M.tuberculosis.[10] It suppresses the growth of most INH-and streptomycin-resistant tubercle bacilli. About 75

to 80% of orally administered ethambutol is absorbed from the gastrointestinal tract. A single dose of 15 mg/kg, produces a plasma concentration of 5 ug/ml at 2-4 hours.[10] Red blood cells may serve as a depot from which the drug enters the plasma. In patients with normal renal function, its half-life is four hours.

The most frequent and serious side effect of ethambutol is optic neuritis. Symptoms include blurred vision, central scotomata and red-green color blindness. This adverse effect is dose-related. Its use is not recommended for children under 13 years of age because of inability to test their visual acuity reliably.[8]

It is used in the treatment of tuberculosis of various forms when given simultaneously with INH. It has replaced aminosalicylic acid because of lower incidence of toxic side effects and better acceptance by the patients.

It has been reported to cause hyperuricemia.

E. Streptomycin (SM)

The first clinically effective drug to become available for the treatment of TB, streptomycin was isolated from a soil organism in 1943.[13] From 1947-1952, it was the only effective drug available to cure the disease. It is bactericidal in the extracellular alkaline environment.

Peak serum concentration of 40 ug/ml is achieved within one hour of intramuscular administration of a dose of 15 mg/kg. Half-life is approximately 5 hours. It does not enter normal biologic membranes and therefore it enters only in the presence of inflammation.[8,10]

Streptomycin causes vertigo, ataxia and hearing loss due to its effect on the 8th cranial nerve.[13,15] Older persons have a higher risk of developing ototoxicity and nephrotoxicity from streptomycin. Because of the inconvenience and pain brought about by intramuscular injections, patients usually seek alternative treatment.

Bacterial Resistance:[10]

Selection for resistant tubercle bacilli occurs in vivo as it does in vitro. Large populations of all strains of tubercle bacilli include a number that are markedly resistant because of mutation.

The longer the therapy is continued, the greater is the incidence of resistance to streptomycin.

II. Second line anti-tuberculosis drugs

A. Ethionamide[8,16]

Ethionamide is a synthetic alpha-ethyl derivative of thioisonicotinamide. Administration of 1 gm. of the drug yields peak concentrations in plasma of about 20 ug/

ml in three hours. It has a shorter half-life than INH. Because of gastrointestinal intolerance, about 50% of patients hardly tolerate a single dose larger than 500 mg.

It is rapidly and widely distributed. It inhibits acetylation of isoniazid in vitro. Multiplication of human strains of M.tuberculosis is suppressed by concentrations ranging from 0.6 to 2.5 ug/ml. Resistance can develop rapidly in vivo.

B. Cycloserine

It is a drug used in certain limited situations. Orally, cycloserine is rapidly absorbed. Peak concentrations in plasma are reached 3 to 4 hours after a single dose.[16,13] It is distributed through out body fluids and tissues. There is no appreciable blood-brain barrier to the drug.[14] The drug may accumulate to toxic concentrations in patients with renal insufficiency.[16,10]

It should be used only when retreatment is necessary or when microorganisms are resistant to other drugs.[10,5] When employed to treat tuberculosis, it must be administered with other effective agents.

C. Kanamycin

It is an aminoglycoside which inhibits the growth of M.tuberculosis in vitro.[8]

This drug is the least often used of the injectable antituberculosis agents in the Philippines. The usual daily dose is 15-30 mg/kg IM with a maximum daily dosage of 1 gm.[13] Auditory toxicity is the most common side effect[8,10] and thus regular audiometry is recommended while patients are on this medication. Renal toxicity also occurs and due to such, serum creatinine monitoring is strongly advised.

D. Morphazinamide

A pyrazinamide-derivative, this drug is used as a second line anti-tuberculosis agent.

Chemotherapy of Tuberculosis

The availability of effective drugs has changed the management of tuberculosis that majority of the patients are presently seen in out-patient or ambulatory setting. An important step in choosing an effective combination of antituberculosis drugs is to obtain the patient's profile. The kind of drug, combination of drug, duration, dose and frequency of intake will depend on certain important factors. For instance, age and weight determine the dose of drug(s) to be taken by the patient. Lifestyle factors like alcohol intake will predict compliance and increase drug toxicity.[13]

To prevent development of resistance to antituberculosis drugs, it is believed that treatment must include at least two drugs to which the bacteria are sensitive.[8]