CHAPTER 1

INTRODUCTION

Background and Rationale

In tropical developing countries, tuberculosis is still a major health problem. As Thailand is one of them, it is not surprising that respiratory tuberculosis is the second cause of death in Bangkok Metropolis in 1982-1983 (1) and about 5 percent of the adults in India and Thailand have pulmonary foci of infection (2). So, central nervous system tuberculosis is not uncommon in these countries.

Tuberculous meningitis is a highly fatal disease. Death usually occurs within 6 to 8 weeks if the disease is not properly treated. Since the advent of streptomycin and isoniazid, with early diagnosis and treatment, the recovery rate may reach 90 %. However, if treatment is not instituted until the disease has reached the late stage, the survival rate is only 25-30 % (3).

Tuberculous meningitis is still a serious problem in developing countries (4,5) because of its high mortality rate and severe residual damage due to the late diagnosis of the disease and the improper of therapy. This is the first reason for this study to be carried out.

In any therapeutic regimen of tuberculosis, a combination of at least two drugs must be used to prevent the emergence of drug-resistance strains (6). The important factor in determining efficacy of antituberculous drugs in treating tuberculous meningitis is the ease

which the drug passes the blood-brain barrier either in normal or inflamed meninges (7,8,9). The percent penetration of antituberculous drugs into the cerebrospinal fluid (CSF) are shown in Appendix 1. Streptomycin penetrates poorly into the CSF (10,11,12). In experimental animals and man, concentrations in CSF are less than 10 % of those in plasma in the absence of meningeal inflammation, this value may approach 20 % when there is meningitis (12). Cerebrospinal fluid concentrations of isoniazid are about 20 % of those in the plasma in the absence of meningeal inflammation (11,13,14) and may increase up to 90-100 % of serum concentrations in patients with tuberculous meningitis (10,11). Ethambutol does not appear in the CSF of normal subjects given the drug by mouth, but it does enter the CSF of patients with tuberculous meningitis. After a dose of approximately 25 mg per kg of body weight, concentrations of ethambutol in the CSF of these patients range from 1 to 2 mcg per ml (9) or vary from 10 to 50 % of simultaneous serum concentrations (11). Like isoniazid, rifampin diffuses well into CSF in meningitis attaining concentration of 0.23 to 0.33 mcg per ml (14) or 10 to 20 % of the serum concentration (10). However, in patients without meningitis, rifampin may not be detectable in the CSF (11). Pyrazinamide penetrates the blood brain barrier very readily, concentrations in the CSF at 5 hr. averaging is 50 mcg per ml and identical to the concomitant serum concentrations (8). Nevertheless, concentrations of the antituberculous drugs in the CSF are mentioned only in a few publications. In Thailand, the penetration of antituberculous drugs in tuberculous meningitis has never been studied before. This is the second reason for this study.

Although steroids have been used in conjunction with antituberculous drugs for the treatment of tuberculous meningitis since the 1950's (15), the use of them has been controversial. Anyway, several studies have shown that the combination of steroids with antimicrobial drugs seems to be more effective in reducing mortality than treatment with antimicrobial drugs alone (16,17,18). Their value in reducing cerebral edema appears generally accepted, but the role in reducing or preventing the development of the basal exudation and fibrosis and the arteritis which results in cranial nerve palsies, hydrocephalus, and cerebral infarction is questioned (19,20). Furthermore, steroid treatment carries three additional problems; a) It suppresses the usual clinical and cerebrospinal fluid responses to infection, making the evaluation of the response too difficult. b) It may mask other infections, including secondary bacterial meningitis. c) There is also a risk that reducing the permeability of the blood-brain barrier towards normal may reduce the transport of antituberculous drugs to the brain and CSF (20). So, the last point of the study may involve the use of steroids in conjunction with antituberculous drugs in comparison with antituberculous drug alone.

Objectives

1. To determine cerebrospinal fluid and simultaneous serum concentrations of four antituberculous drugs ; i.e. isoniazid, pyrazinamide, rifampin, and streptomycin, at various intervals in tuberculous meningitis patients receiving the combination of these four drugs during hospitalization.

2. To study the correlation of cerebrospinal fluid and serum

concentrations of each antituberculous drug.

3. To compare cerebrospinal fluid concentrations and serum concentrations of each antituberculous drug in patients receiving the combination of steroids and antituberculous drugs with patients receiving antituberculous drugs alone.

4. To evaluate the clinical use of the combination of these four drugs in tuberculous meningitis patients studied above during hospitalization.

Significance of the study

1. The determination of cerebrospinal fluid as well as serum concentrations of the antituberculous drugs will be useful in treatment of tuberculous meningitis as follows:

1.1 The cerebrospinal fluid concentrations of each antituberculous drug will be compared with minimum inhibitory concentration (MIC) against Mycobacterium tuberculosis of that drug.

1.2 The cerebrospinal fluid as well as serum concentrations will show the ability of antituberculous drugs in penetration into CSF

The results from the study may be a guideline for physicians in choosing the appropriate regimen of antituberculous drugs in treatment of the disease and may decrease the expenses of treatment

2. The correlation between CSF and serum concentrations of each antituberculous drug will help the physicians in estimating CSF concentrations from serum concentrations of the patients in whom lumbar puncture can not be performed.

3. Effects of steroids to CSF concentrations as well as serum concentrations of each antituberculous drug, if any, will help the physicians in deciding to use steroids in tuberculous meningitis patients. In addition, it may be a preliminary study for other workers to set further studies.