CHAPTER II

REVIEW OF THE LITERATURE

TUBERCULOUS MENINGITIS

More than 200 years after the first description by Sir Robert Whytt in 1768, tuberculous meningitis (TBM) continues to be a serious problem in the developing countries including Thailand. Even though effective chemotherapy has been introduced, the mortality rate is still high and severe residual damage still occurs in the survivors. Treatment of tuberculous meningitis remains a challenge to the medical profession.

Pathogenesis and Pathology

Tuberculous meningitis is caused by acid fast organism, Mycobacterium tuberculosis (21). In most cases, the infection is now resulted from the human type organism (22,23). Tuberculous meningitis is always secondary to tuberculosis elsewhere in the body. The primary focus of infection is most commonly in the lungs, but it may be in the lymph glands, bones, nasal sinuses, gastrointestinal tract or any other organ in the body (22,24). In the past, tuberculous meningitis was considered a disease of pediatrics and young children, but nowadays it occurs at any age and is equally frequent in adults (22,24,25).

It is now believed that in most cases tuberculous meningitis is due to an infection of the meninges from a caseous focus in the brain. The bacillus is carried to the central nervous system (CNS) by the

blood stream, usually from a focus in mediastinal or abdominal lymph nodes, but it can derived from any infected organ of the body, e.g. bones, joints, lungs, and genito-urinary tract (23,26). Then the granular formation occurs in the meninges, following by the rupture of one or more of these foci and the discharge of bacilli into the subarachnoid space (14,21).

On naked-eye examination, the brain is usually pale and the convolutions are somewhat flattened. A yellowish gelatinous exudate is found matting together the leptomeninges at the base and extending along the lateral sulci. Miliary tubercles are visible on the leptomeninges, being most conspicuous along the vessels, especially the middle cerebral artery and its branches. Microscopically the tubercles is composed chiefly of mononuclear cells, lymphocytes, plasma cells, macrophages and fibroblasts with an occasional giant cell. The substance of the nervous system shows little inflammatory reaction, but marked toxic degeneration of nerve cells. As a result of prolonged chemotherapy the basal exudate becomes intensely hard and woody, the large arteries passing through it show an arteritis which lead to cerebral and brainstem infarction. Adhesions may cause hydrocephalus, or obstruction of the spinal subarachnoid space (14,22,23,24,26).

Signs and Symptoms

The onset is almost always insidious so that the disease is usually not suspected in its first stage characterized by such nonspecific manifestation (26,27). In children,lassitude, anorexia, loss of weight, and intermittent vomiting are prominent. In adults,the early manifestations are usually headache, lethargy, malaise, decreased

appetite, loss of weight, fever and a feeling of ill health. This prodromal phase usually lasts two or three weeks and diagnosis is often delayed until the patient has reached the second stage (14,21, 22). With progressive invasion of the meninges, headache increases in severity and symptoms of meningeal irritation such as neck stiffness, Kernig's sign, etc., occur. Fever, if previously absent, usually now appears but is rarely high. The temperature, which is often markedly irregular, does not usually rise much above 38.9° c. Because of the inherent chronicity of the disease, signs of cranial nerve involvement (usually ocular palsies, less often facial palsies or deafness) may be present in this stage. Occasionally, the disease may present with a focal neurologic deficit such as hemiparesis, or with signs of raised intracranial pressure, and rarely with symptoms referable to the spinal cord and nerve roots. This second stage evolves over a period of a week or two, sometimes longer. In the terminal stage, the patient is characterized by confusion and progressively deepening stupor and coma, coupled with cranial nerve palsies, pupillary abnormalities, and rising pulse and respiratory rates (21,22,26).

The Cerebrospinal Fluid

The cerebrospinal fluid pressure is normal during the prodromal phase, but ultimately it will increase. Examination usually reveals turbid to cloudy fluid (or it may even be clear). There is an increase in the number of cells, usually between 25 to 500 per cumm. In the acute form of this disease the cell count is more than 500 per cumm, sometimes up to 1000 per cumm or more . These may be a mixture of mononuclear cell and polymorphonuclear leukocytes with neutrophils predominating during the first week and lymphocytes thereafter.

The protein content of the CSF is always elevated between 100 to 200 mg % in most cases, but much higher if CSF blockage occurs around the spinal cord. The sugar level is usually decreased below 40 mg %. Acid-fast smears should be performed on all spinal fluids, but often it is not positive (14,21,22,28,29).

Diagnosis

No single criteria or test alone can be used to exclude this disease. All clinical and laboratory findings must be evaluated together in the investigation of the patient (30). In the early stage it is easy to miss the diagnosis since the signs and symptoms do not necessarily point to the nervous system at all (26).

The diagnosis of tuberculous meningitis is usually based on characteristic cerebrospinal fluid findings : a pleocytosis with a predominant lymphocytic response, a decrease in glucose level, and an elevation of protein content. However, about 20 to 30 % of patients will not show these typical findings. The diagnosis is considered more definite if there is a history of contact with a known tuberculous patient, radiological evidence of pulmonary tuberculosis, and a positive tuberculin skin test. It is often difficult to detect an acid fast bacilli on a cerebrospinal fluid smear, but if it is demonstrated it may be an importance diagnostic clue. Clearly, the most specific diagnostic test is the culture of the cerebrospinal fluid, but usually it takes some time for the organism to be recovered from the cerebrospinal fluid culture and not all patients will have a positive culture (31,32).

Differential Diagnosis

There are a variety of infections of the central nervous system with similar clinical presentations and spinal fluid findings as tuberculous meningitis. Once a diagnosis of meningitis has been made, it must be distinguished from the other meningeal infections. In all doubtful cases lumbar puncture should be performed and the characteristics of CSF may differentiate the type of meningitis as shown in Appendix 2.

Bacterial or pyogenic meningitis starts more acutely, the signs of meningeal irritation are more prominent, and the spinal fluid response is polymorphonuclear in type. The organism responsible for the disease will be found in smears and on culture (24,26).

The clinical picture and cerebrospinal fluid findings in cryptococcal meningitis may be identical with those of tuberculous meningitis. The differential can be made by finding the budding yeast organisms by gram stain, indian ink preparations, cryptococcal antigens, or culture on blood agar or Sabouraud's medium (14,24,26).

Meningeal involvement in the course of viral infections such as mumps, lymphocytic choriomeningitis and the various forms of viral encephalitis may give a clinical picture similar to that of tuberculous meningitis. In these cases no organisms can be found in the spinal fluid and the cerebrospinal fluid sugar content is almost always normal (24,26).

In parasitic meningitis the sugar content in CSF is normal and the cells in CSF are eosinophils. Rarely, the causative parasites can

be seen in the CSF (31).

Acute syphilitic meningitis is rare. The normal or relatively normal sugar content in CSF and the positive serological reactions in both blood and CSF make the diagnosis of syphilitic meningitis relatively easy (24,26).

Diffuse involvement of the meninges by metastatic tumors (carcinoma or sarcoma) or by gliogenous tumors may produce mental confusion and meningeal signs. The cerebrospinal fluid may contain a number of lymphocytes and polymorphonuclear leukocytes and a reduced sugar content. Tumor cells can sometimes be seen and organism will, of course, be absent (24,26).

Prognosis

Tuberculous meningitis is a highly fatal disease. Prior to the advent of streptomycin and other antituberculous drugs there was no effective therapy. The disease can be considered as 100 % fatal and death usually occurs within three to four weeks of the onset (22,24,26). With the introduction of streptomycin, survival increased to 25 to 36 per cent of treated cases; the addition of para-aminosalicylic acid (PAS) to the regimen further increased survival to 51 and 73 percent of cases reported in two series. The addition of isoniazid (INH) increased survival even further, to about 85 per cent (14).

Antituberculous therapy should be instituted when clinical suspicion and laboratory data suggest the diagnosis. It is not necessary to wait for culture confirmation. Early diagnosis and institution of adequate antituberculous therapy enhance the chances of survivals(19,21,33).

The level of consciousness at the time of presentation is one of the other important prognostic signs, for the greater the depression the worse the outcome. The patients who progress to the later stages of the disease often die or are left disabled (14,34).

The prognosis is influenced considerably by the age of the patients. The mortality rate rises with increasing age. The prognosis is also related to the presence of associated diseases, nutritional status, presence and state of tuberculosis in other organ systems, and immune status (14,35,36,37). Even with appropriate therapy, residual deficits secondary to the fibrotic inflammatory exudation may occur(14). Relapses occasionally occur after a period of months or even years in apparently cured cases (24).

Treatment

All patients with a diagnosis of tuberculous meningitis should be considered emergency cases and treatment should be started as soon as the diagnosis in even suspected, especially in patients who are stupurous or comatose. Treat symptoms as they arise, maintain good nutrition and adequate fluid intake are important. For good results, the patient should receive simultaneously appropriate antituberculous drugs, proper management of increased intracranial pressure, and other essential supportive treatment. Rehabilitation of the patient should be started early.

The ideal antituberculous drugs for the treatment of tuberculous meningitis should provide an adequate cerebrospinal fluid concentration and be effective against the causative organisms, e.g. isoniazid,

rifampin, streptomycin, ethambutol and pyrazinamide (3,31).

DRUG TREATMENT IN TUBERCULOUS MENINGITIS

Antituberculous drugs

Tuberculous meningitis was a frequent and invariably fatal disease three decades ago. With the advent of streptomycin in 1947 it became possible to treat patients with tuberculous meningitis. At that time streptomycin was the only antibiotic available and no one knew the best way to use it. From 1948-1950, streptomycin treatment was more standardized and used in prolonged intramuscular and intrathecal courses. It did save a few patients but intrathecal streptomycin caused deafness in about 50 % of the survivors. (27,38,39)

In 1950, the combination of streptomycin with para-aminosalicylic acid (PAS) was introduced by Lorber (39). This combination led to a considerable decrease in the number of intrathecal injections, but, even so, 10 out of 48 children required the frightening total of 135 injections. The result was much better than treatment with streptomycin alone : 35 (73 %) are alive and 30 of them (63 %) had no neurological sequelae. Of 82 children who were treated with streptomycin alone, 30 (36 %) are alive, as compared with 73 % of 48 treated with streptomycin and P.A.S. and 62 (76 %) had residual neurological sequelae (39).

When isoniazid became available in 1952, the outcome of therapy improved, Streptomycin by the intrathecal route has been much reduced and the incidence of deafness among the survivors has decreased sharply. So, isoniazid is a valuable addition to other drugs in the treatment of

tuberculous meningites. From a report on a controlled trial of isoniazid in the treatment of tuberculous meningitis by Lorber (40), 22 patients who were conscious on admission were allocated by random sampling to two treatment groups, 10 being controls and 12 being given isoniazid. Eight of ten controls and eleven of twelve-treated patients survived. None of the patients had serious sequelae and none are deaf. Patients in the INH group required fewer intrathecal injections of streptomycin (average 65) compared with the controls (average 90).

With the introduction of isoniazid, the combination of isoniazid, streptomycin and P.A.S. was used. Between 1952 and 1958 Lorber (38) treated 80 new cases with this triple-drug therapy and he progressively reduced the arbitrary minimum number of intrathecal streptomycin injections from courses of 45 to 25, then to 20, and to only 10 injections. The overall survival rate in the 80 isoniazid-treated children is 83 %. Of the 55 who were conscious on admission, 52 (95 %) survived and 50 (91 %) had no mental or neurological sequelae. Out of 25 who were in the advanced stage on admission only 14 (56 %) survived. In 1960, treatment of tuberculous meningitis in children was suggested by American Trudeau Society (41). It was the opinion of the Committee that all patients with tuberculous meningitis should receive triple-drug therapy, streptomycin being given daily (at least for a few weeks) and isoniazid in comparatively high dosage. Treatment with isoniazid and P.A.S. should be continued for a minimum of one year and in many cases longer, although streptomycin should be discontinued with in a month after satisfactory clinical response. More information about the treatment of tuberculous meningitis was recommended in 1969 by the American Thoracic Society (42). The recommended therapy consisted of isoniazid,

streptomycin, and para-aminosalicylic acid. All patients should receive isoniazid at least 20 mg/kg/d at the start to a maximum of 500 mg/d. If the patient is vomiting, it is important to assure the retention of isoniazid by intravenous or intramuscular administration. Streptomycin, given 1 gm intramuscularly, and para-aminosalicylic acid 200 mg/kg/d orally were given along with the INH. Streptomycin was given daily at first. The frequency might be reduced to twice or three times a week as the clinical condition improved. It was discontinued entirely as soon as possible. Isoniazid and PAS should be continued for at least two years.

Because of the increasing frequency of isoniazid and streptomycin resistant strains at the hospital, the drug regimen was expanded. Ethambutol orally 15 mg/kg/d was added to the drug regimen and the patients were successfully treated with combined chemotherapy including ethambutol (43,44). Girgis et al (43) studied 86 patients with tuberculous meningitis admitted to the Abbassia Fever Hospital, Cairo, Egypt. The data indicated that ethambutol can be used as a companion drug to isoniazid and streptomycin in the treatment of the disease. Of the 86 patients treated, 55 (64 %) survived and 31 (36 %) died. There was no significant difference in mortality rates between the two groups. Of the 42 patients in the ethambutol group 16 (38 %) died compared to 15 (35 %) out of 44 in the PAS group. It was apparent from this trial that both regimens were equally effective in the treatment of the disease.

Rifampin was developed and initially tested in Italy in 1963. Because of its bactericidal action on Mycobacterium tuberculosis in vivo and vitro, rifampin has been introduced for the treatment of tuberculous meningitis. Many clinical trials indicating the effective-

ness of rifampin in the treatment of the disease were reported (4,5, 27,45,46,47,48). Visudhiphan and Chiemchanya (5) compared patients treated with isoniazid and rifampin with a second set of patients given a standard regimen of isoniazid, streptomycin and PAS. Of the 20 patients in the first group, 19 survived and one died. Twelve patients recovered from the disease without any significant neurologic defect. Seven patients had moderate to severe neurologic sequelae. Among the 13 patients in the second group, four were dead. Only three patients recovered with a completely good condition. The remainder had either single or multiple neurologic defects. Rifampin reduced the mortality and morbidity of the disease in children without causing serious side effects. Rahajoe et al (47) also confirmed its therapeutic efficacy in patients with tuberculous meningitis. They studied in two groups of patients. Twenty two children were treated with isoniazid, streptomycin and rifampin (Group 1) and nineteen were treated with isoniazid, P.A.S. and streptomycin (Group II) for at least 18 months. Both groups received corticosteroids at the beginning of treatment. The rate of recovery in the first two months of treatment was slightly more rapid in group 1 than in group II and neurological sequelae were less frequent in group 1 than in group II, but the differences between the groups were not statistically significant. There was very little difference in the death rate. A high incidence of jaundice was found amongst the children who received rifampin.

Various combinations of drugs have been advocated and there are so many drug regimens in the treatment of tuberculous meningitis but the optimal antimicrobial regimen for therapy of the disease is unknown (49). The most effective treatment in the early stage of active

inflammation is a combination of streptomycin, isoniazid, pyrazinamide and/or rifampin. Fox and Mitchison (50) described isoniazid and rifampin as "complete" bactericidal drugs against the entire population of M. tuberculosis. Streptomycin and pyrazinamide are synergistic; streptomycin, as active in tissues with an alkaline pH, pyrazinamide, as active in an acid pH. Then streptomycin and pyrazinamide are said to be one-half bactericidal each and only together are considered to form a single bactericidal drug. However, combination of pyrazinamide in the above regimen is recommended only in the first two months of treatment because incidence of hepatitis is high with long term administration. After a period of 3 to 6 months streptomycin can be discontinued and isoniazid and rifampin continued for at least 2 years. Alternatively combination of isoniazid and ethambutol are equally effective with isoniazid and rifampin. Rifampin is particularly useful in isoniazid resistant organisms. Since these newer drugs are expensive, while cost of drug treatment is the main concern and if toxic effects of these drugs appear, thiacetazone in combination with isoniazid can be used (28). Due to uncompliance of the patients in long term therapy, a regimen of isoniazid and rifampin may also employed for at least six months with or without continuing isoniazid therapy for another year (14). The other second-line drugs such as ethionamide, cycloserine, viomycin, capreomycin, and kanamycin may be employed in the cases resistant to isoniazid. The recommended doses for antituberculous drugs for adults and children (11,13,51) are summarized in Appendix 3. Antituberculous drugs may be classified as the first-line (primary, major) antituberculous drugs (include isoniazid, rifampin, ethambutol, and streptomycin) and the second-line (secondary, minor) antituberculous drugs (include para-aminosalicylic acid, pyrazinamide, cycloserine,

ethionamide, viomycin, capreomycin, and kanamycin). The pharmacokinetics of each drug are briefly discussed as follows.

Isoniazid

Isoniazid has been the most effective agent in the treatment of tuberculous meningitis. Since its introduction in 1952, isoniazid has significantly reduced morbidity and mortality of the disease (18). Due to its low toxicity and excellent penetration into the cerebrospinal fluid, isoniazid has become the mainstay of chemotherapy.

Isoniazid is readily absorbed when administered either orally or parenterally. Peak plasma concentrations of 3 to 5 mcg per ml develop 1 to 2 hours after oral ingestion of usual doses and these decline to 50 % or less within six hours (13,51). The drug diffuses readily into all body fluid (including ascitic, pleural and cerebrospinal fluid), tissues, organ and excreta (sputum, saliva and feces). Cerebrospinal fluid concentrations of the drug may be 20 % of serum levels in the absence of meningeal inflammation (11,13) and may increase to be about 90 % of the concomitant serum concentrations in patients with tuberculous meningitis (8,52). It also passes into the placental barrier and into milk in concentrations comparable to those in plasma. It is metabolized in the liver by acetylation which is genetically determined. From 75 to 95 % of a dose of isoniazid is excreted in the urine in 24 hours, entirely as metabolites of the drug. The clearance of isoniazid 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 (13).

Rifampin

Rifampin,the newest drug for the treatment of tuberculous meningitis, has bactericidal activity against M. tuberculosis. The drug in combination with isoniazid has been highly effective in treating the disease, but resistance rapidly develops when it is used alone.

Rifampin, 600 mg administered orally, is almost completely absorbed and achieves mean peak serum concentration of 7 mcg per ml (with ranges of 6 to 32 mcg per ml) within one to four hours. Food interferes with absorption. It is about 80 % protein bound but very lipid soluble. It is distributed throughout the body and is present in effective concentrations in many organs and body fluids including the cerebrospinal fluid. Cerebrospinal fluid concentrations of rifampin in patients with tuberculous meningitis approach 20 % of the serum concentrations which represents the fraction of drug in serum that is not protein bound. These concentrations may be detected as early as 2 hours following an oral dose and may remain above the minimal inhibitory concentration of M. tuberculosis for as long as 1 to 2 months with continuous therapy (53). Sippel et al (54) also reported that high CSF concentrations were obtained within 3 hours and maintained for at least 24 hours when 25 mg of rifampin per kg of body weight was administered orally to patients with tuberculovs meningitis who had not received previous antituberculous chemotherapy. No rifampin could be detected in the 3-hour CSF specimens taken from control subjects (54). On the other hand, Ostrow et al found that it crossed the blood-brain barrier in healthy individuals, but it did so much more freely in patients suffering from tuberculous meningitis (55). Moreover, rifampin crosses the placenta and appears in breast milk.

Rifampin is metabolized in the liver to its deacetylated form, which is also active against M. tuberculosis. After passing through the liver, about 40 % is excreted in bile and undergoes enterohepatic circulation. Up to 30 % of a dose of the drug is excreted in the urine, half of this may be unaltered antibiotic. Adjustment of dosage is not necessary in patients with impaired renal function (13,51). The half-life of rifampin varies from 1.5 to 5 hours, but decreases by 40 % over the first two weeks (51).

Ethambutol

Ethambutol is a tuberculostatic agent which acts against dividing microorganism only. It is given in combination with other antimicrobial agents to delay the onset of bacterial resistance.

About 70 to 80 % of an orally administered dose of ethambutol is absorbed from gastrointestinal tract. A single oral dose of 15 to 25 mg per kg of body weight can produce peak serum levels of 2 to 5 mcg per ml within 2 to 4 hours after administration. Cerebrospinal fluid concentrations of the drug are not detectable in normal persons without meningitis (9), but ethambutol do enter the CSF of patients with tuberculous meningitis. After a dose of approximately 25 mg per kg of body weight, Place et al (9) found that concentrations of ethambutol in CSF ranged from 1 to 2 mcg per ml in seven patients with tuberculous meningitis while cerebrospinsl fluid concentration in majority of cases of patients with tuberculous meningitis in Bobrowitz ID's study (56) was 1 mcg per ml or higher.

Only 20 % of the drug is metabolized by the liver, changing to aldehyde and finally to dicarboxylic acid. The drug has a half-life

of 3 to 4 hours. Approximately 50 and 25 % of ethambutol is excreted unchanged in the urine and feces respectively while an additional 10-15% appears in the urine as metabolites (11).

Streptomycin

Streptomycin is an aminoglycoside antibiotic. It should never be used as the sole therapeutic agent due to the rapid development of bacterial resistance to the drug (10).

Streptomycin is poorly absorbed from the gastrointestinal tract and therefore it must be administered parenterally in order to achieve systemic therapeutic effects. A dose of 1 g given intramuscularly to an adult will produce peak serum concentrations of 10 to 20 mcg per ml within 1 hour. The average serum half-life is 3 hours. Streptomycin is distributed in all extracellular fluids and cross the placental barrier. It does not achieve significant levels in the cerebrospinal fluids in normal patients, although penetration is enhanced in the presence of inflamed meninges, only low levels are achieved(11,51). The drug is excreted primarily by glomerular filtration in the kidneys, with approximately 75 % of a dose excreted in the urine in 24 hours. When renal function is impaired, accumulation and subsequent toxicity may occur. So, monitoring of renal function and appropriate dosage adjustments are essential to avoid significant nephrotoxicity and/or ototoxicity (10,11,51).

Para-aminosalicylic acid (PAS)

Para-aminosalicylic acid is bacteriostatic agent which acts by inhibition of folic acid metabolism. It inhibits the onset of bacterial

resistance to streptomycin and isoniazid (11,13,51).

PAS is readily absorbed from the gastrointestinal tract. A single oral doses of 4 g of free acid produces peak plasma concentrations of about 75 mcg /ml within 1.5 to 2 hours. It is widely distributed and reaches high concentrations in pleural fluid and caseous tissue, but low levels are found in CSF. The half life of PAS is about one hour. It is metabolized in the liver which over 50 % is acetylated. Over 80 % of the drug is excreted through the kidneys as metabolite and free acid. Excretion is retarded in the presence of renal dysfunction (11,13,51).

Pyrazinamide

Pyrazinamide is bacteriostatic against Mycobacterium tuberculosis. It is well absorbed from the gastrointestinal tract. The oral administration of 1 g produces plasma concentrations of about 45 mcg per ml at 2 hours and 10 mcg per ml at 15 hours. It is widely distributed throughout the body, including cerebrospinal fluid (13,51). The cerebrospinal fluid concentrations of the drug are about 100 % of serum concentrations in normal and inflamed meninges (8,51). The drug is primarily metabolized by the liver and excreted by renal glomerular filtration (13,51).

Cycloserine

Cycloserine inhibits the early formation of microbial cell wall (11,51). When given orally, cycloserine is rapidly absorbed. Peak plasma concentrations are reached 3 to 4 hours after a single dose and are in the range of 20 to 35 mcg per ml in children who receive 20 mg

per kg; only small quantities are present after 12 hours. In adults, doses of 750 mg, given at 6-hour intervals, plasma concentrations is excess of 50 mcg per ml. Cycloserine is distributed throughout body fluids and tissues. Cerebrospinal fluid concentrations in all patients are approximately the same as those in plasma (13,51). Approximately 35 % of the drug is metabolized. About 50 % of a parenteral dose of cycloserine is excreted unchanged in the urine in the first 12 hours; a total of 65 % is recoverable in the active form over a period of 72 hours. Renal insufficiency will lead to toxic accumulation which may be removed by dialysis (13,51).

Ethionamide

Ethionamide is bacteriostatic against M. tuberculosis which exerts it effects most likely by inhibiting protein synthesis (11). The oral administration of 1 g of ethionamide yields peak concentrations in plasma of about 20 mcg per ml in 3 hours and the concentration at 9 hours is 3 mcg per ml. It is rapidly and widely distributed. The concentrations in the blood and various organs are approximately equal. Significant concentrations are present in CSF. The drug is metabolised in the liver and less than 1 % is excreted in the urine (13,51).

Viomycin

Viomycin inhibits protein synthesis by M. tuberculosis. The absorption and the excretion in man are similar to those of streptomycin. Absorption from the gastrointestinal tract is limited. The intramuscular injection of 25 to 50 mcg per kg produces maximal plasma concentrations in 2 hours. A large proportion of a dose of the drug is recoverable in the urine. Penetration into CSF is poor (13).

Capreomycin

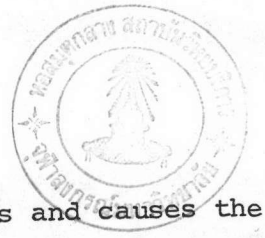
Capreomycin active against human strains of M. tuberculosis. Capreomycin sulfate is not absorbed in significant quantities from the GI tract and must be administered parenterally. Peak serum concentrations following IM administration of 1 g are cheived in one to two hours. Low serum concentrations are present at 24 hour. The drug is excreted essentially unaltered which 52 % is excreted in the urine within 12 hours (13,51).

Kanamycin

Kanamycin has also been employed to treat human tuberculosis in combination with other effective drugs. Since the therapy of this desease is long and involves the administration of large total doses of the drug, with the risk of ototoxicity and nephrotoxicity, it should be used only to treat patients who harbor microorganism that are resistant to the more commonly used agent (13). Its mechanism of action and pharmacokinetics is similar to those of other aminoglycosides.

Corticosteroids

It appears that antimicrobial therapy alone did not result in satisfactory recovery rate in tuberculous meningitis. So, various adjuvants and neurosurgical techniques have been used in combination with antituberculous drugs to improve the outcome. The purpose of any adjuvant to the chemotherapy of tuberculous meningitis is to combat the dense inflammatory exudate and granulation tissue that frequently obstructed at the anterior of the basal cisterns and at the sylvian fissures. This exudate prevents free access of the



antibiotics to the organisms and causes the typical squints, mental changes and the communicating hydrocephalus, which was,in many cases, the ultimate cause of death. Moreover, the neighbouring blood vessels develop an obliterative arteritis with consequent infarction of brain (57,58). Intrathecal streptokinase-streptodornase, purified protein derivative of tuberculin and fibrinolytic agents which were directly instilled into the ventricles through frontal burr-holes have all been tried in an effort to delay or prevent the formation of tuberculous exudate on the meninges (57). Recently the enzyme hyaluronidase has been shown to be effective in the management of spinal arachnoiditis, communicating hydrocephalus and optochiasmatic arachnoiditis complicating the course of tuberculous meningitis (28,59,60).

Corticosteroids, as an adjuvant to usual chemotherapeutic agents, were introduced in the management of tuberculous meningitis in 1951 by Kinsell (61). Since then, a number of studies have confirmed their utility while others have refused in the routine administration of steroid for the disease.

Weiss and Flippin (37) in 1965 as well as Crocco, et al (35) in 1980 found no statistical difference between their steroid-treated patients and non-steroid treated patients, but these were studied in uncontrolled manner. In 1966, Hockaday and Smith (58) concluded that there was no place for the routine use of cortisone or its analogues in tuberculous meningitis. The opinion that intrathecal steroids did not have any specific role in the management of the disease was also supported by Freiman and Geefhuysen (62) and Gourie-Devi, et al (60,61) Moreover, it carries a risk of convulsion and paradoxical produces adhesive arachnoiditis (60).

On the other hand, many authors believed that the drug may be helpful in the treatment of tuberculous meningitis. Shane and Krzyski (57) reported that the addition of corticotrophin or corticosteroids to antimicrobial therapy resulted in improved recovery figures, rapid return of the spinal fluid findings to normal, and absence of neurological sequelae. Kendig, et al (63) found that cortisone may be of value in the prevention of CSF block associated with the disease, but extreme caution is indicated in the cases of pulmonary tuberculosis. Choremis, et al (64) noted that patients improved more rapidly when given steroids, but mortality was unchanged. Misra and Khanna (65) also reported the effectiveness of steroids in a study of forty patients receiving steroids and fifteen controls but no matching procedure was utilized to ensure comparability of the groups. However, many workers could not assess the benefit of steroid therapy and restrict their use to the more severely ill patients or those with spinal block. So, Lorber (38) and Idriss, et al (17) recommended to use systemic corticosteroids in children under 1 year of age or in those who are unconscious on admission and intrathecal hydrocortisone in threatened or established spinal block. Lorber (38) recommended that the oral dose of cortisone is up to 300 mg daily, gradually reducing to 100 mg daily or its equivalent if any other corticosteroid was used while the dose of hydrocortisone intrathecally was 10-25 mg according to age.

Since several studies have shown that giving steroids along with antimicrobial drugs seems to be more effective in reducing the mortality than treatment with antimicrobial alone (16,17,18,66), corticosteroids are recommended to use in the disease. Escobar, et al (16) recommended that low dose steroids (1 mg/kg of prednisone

daily for 30 days) was used routinely in treating tuberculous meningitis. Low doses of steroids were found to be just as effective as high doses (10 mg/kg of prednisone daily) and produced fewer side effects. Dexamethasone administered intravenously (0.5-1.0 mg/kg/day) in 4 divided doses was given by Idriss, et al (17) with good results in the initial treatment of patients with severely increased intracranial pressure complicating tuberculous meningitis. When administered early, steroids seem to suppress the inflammatory reaction which leads to increased intracranial pressure and cerebrospinal fluid blockage, thus being effective in the management of cerebral edema associated with the disease (63,66). Although steroids reduce mortality, Freiman and Geefhuysen (62) warned that it might increase the incidence and/or severity of sequelae

These published works have failed to clarify the position and even now, the value of corticorsteroids is still not proven. However, at the present time, steroids are still prescribed in most of the cases of tuberculous meningitis. Many authors believe that they could reduce cerebral edema and inflammatory exudate and prevent spinal blocks, particularly in infancy. Nevertheless, the evaluation of corticosteroids is still open to question and should be further studied.