CHAPTER 5

DISCUSSION

I. Studies of Cerebrospinal Fluid and Serum Concentrations of Antituberculous Drugs at Various Intervals During Hospitalization

Cerebrospinal fluid penetration of antibacterial drugs is important in treating central nervous system infections, the timing of which may be critical not only for achieving a cure but also for avoiding late sequelae. There is no single specific variable which dictates how a drug will behave. Physicochemical properties of the drug (lipophilicity, degree of ionisation and molecular size) is one variable that influence the penetration into CSF. Binding by serum proteins also restricts the passage of drugs into the CSF. In addition, cerebrospinal fluid penetration is markedly enhanced by meningeal inflammation, especially for those drugs which are poorly lipid-soluble (76,77).

In Table 1,2 and Figure 1 the levels of isoniazid in the serum and cerebrospinal fluid of the patients indicated that isoniazid crosses the blood brain barrier in the presence of inflamed meninges and an appreciable level is achieved in the cerebrospinal fluid of patients with tuberculous meningitis. Elmendorf *et al* (52) reported that appreciable concentrations of the drug were present in the CSF within 3 hours of an oral dose of 2.0 to 3.0 mg/kg in patients without meningitis and in patients with tuberculous meningitis, the concentrations of the drug in CSF after oral administration were substantially higher than the concentration necessary to inhibit *M. tuberculosis* H 37 Rv in vitro.

Similar to the study of Elmendorf, all concentrations in the cerebrospinal fluid of isoniazid in this study were higher than the MIC (mean = 0.23 mcg/ml) for M. tuberculosis. The overall mean concentration (2.40 mcg/ml) of the drug was 10 times greater than the mean MIC. When the mean concentrations of the drug in each 7-day interval were compared, there was no statistically significant difference between these mean concentration. So, therapeutic concentrations of isoniazid were maintained even though the drug was given more than one month and the clinical signs and symptoms of the patients were improved. In addition, the differences of the mean CSF/serum ratios at various intervals were not statistically significant and the overall mean CSF/serum ratio of isoniazid in CSF was 0.89 ± 0.62 or the mean percent penetration into the CSF of isoniazid was about 89. Likewise, the percent penetration of isoniazid in this study was close to the study of Forgan-Smith et al (8) of which the concentrations in the CSF at 3-6 hours (mean 2 mcg/ml) were 90 % of the concomitant serum concentrations. Hence, isoniazid diffuses very well into the cerebrospinal fluid of the patients with tuberculous meningitis due to the high lipid - solubility and free from protein-binding of the drug. However, further studies should be performed to follow up the levels of the drug in the CSF after hospitalization and until the course of the treatment was terminated.

The correlation between CSF and serum concentrations of isoniazid has not been studied before. In this study, the correlation was not statistically significant with the correlation coefficient of 0.1654 ($p > 0.05$). Therefore, the CSF concentrations of isoniazid cannot be predicted from the serum concentrations.

The first study of pyrazinamide in the cerebrospinal fluid in 28-year-old man with active tuberculous meningitis was reported by Forgan - Smith et al (8). Pyrazinamide penetrated the blood brain barrier very readily, concentrations in the CSF at 5 hour averaging 50 mcg/ml and being identical to the concomitant serum concentrations. The results from this study also revealed that the overall mean concentration of pyrazinamide at 3 hour was 34.78 ± 14.42 and the mean percent penetration into CSF was 91. In addition, the overall mean concentration was above the MIC (mean = 20 mcg/ml) for M. tuberculosis. Some concentrations in the CSF were lower than the MIC since the determination of the drug was done at 3 hour after administration and in 2 patients (PV and PT) the drug was given in three - divided doses. The differences between the mean concentrations at various intervals were not statistically significant so that the therapeutic concentration of pyrazinamide was obtained even when the drug was given more than one month. However, study of the levels of pyrazinamide in the CSF should be further continued in order to determine the penetration into the CSF of the drug in the patients with tuberculous meningitis after hospitalization and until the drug was discontinued.

The correlation between CSF and serum concentrations of pyrazinamide was statistically significant with the correlation coefficient was 0.8922 ($p < 0.05$). There was tendency that higher serum concentrations would cause the higher CSF concentrations. Hence, the CSF concentrations of the drug may be predicted from the serum concentrations by using linear regression equation. This is the first such study of pyrazinamide in this situation.

Rifampin is known to penetrate the cerebrospinal fluid barrier in adequate concentrations in patients with tuberculous meningitis. The concentrations of the drug in the CSF were about 20 % or less of the corresponding serum levels indicating sufficient penetration of the blood brain barrier (8,27,53,54,55,78). The significant concentration of the drug was reached within 3 hours and maintained for 24 hours (53,54). In this study, the overall mean concentration of rifampin was 0.29 mcg/ml which was higher than the MIC for M. tuberculosis and the mean percent penetration into the CSF was 5. The diffusion of rifampin into the CSF not only depends on the free fraction of the drug (the drug is 80 % protein bound) but also a combination of high lipid solubility and a lower degree of ionization at physiological pH (77). Although the concentrations in the CSF were fluctuated from the MIC after the drug was given more than three weeks of the treatment as shown in Figure 3, the mean concentrations in the CSF as well as the mean CSF/serum ratios at various intervals showed no statistically significant differences ($p > 0.05$). Nevertheless, D' Oliveira (53) reported that the therapeutic concentrations in the CSF were maintained during 1 to 2 months of treatment despite decline of the concentration in the course of long - term treatment. He found that after 1 or 2 months of treatment, the CSF concentrations after 3 hours administration were greater than the MIC for M. tuberculosis. In comparison of the CSF concentrations in this study with D' Oliveira's, the CSF concentrations in both studies were nearly the same. However, it is possible that the MICs for M. tuberculosis used in both studies are different. In this study the MIC for M. tuberculosis was averaged from many textbooks. In fact, the MIC should be determined from the culture of M. tuberculosis

obtained from the patients but the organisms were not found in the culture of the patients in this study. However, study on rifampin levels in the CSF should be further continued to confirm the clinical efficacy of rifampin in the treatment of tuberculous meningitis.

It was very interesting that the correlation between CSF and serum concentrations of rifampin was statistically significant with the correlation coefficient of -0.4223 ($p < 0.05$). There might be a lag time of rifampin in penetration into CSF i.e. it reaches a CSF peak one or two hours after the plasma peak. Thus, when the samples were collected at 3 - hour after administration of the drugs, the concentrations in CSF might be higher or lower than the serum concentrations depending on the variation of the time of peak effect in each patient . Nevertheless, the correlation of CSF and serum concentrations of rifampin needed to be further studied.

The penetration of streptomycin across the blood brain barrier is poor and therapeutic levels in the CSF are not attained even in the presence of meningitis (11,12). Forgan - Smith et al (8) reported that concentrations in the CSF of the drug increased from about 3 mcg/ml at 2 hr to 9 mcg/ml at 5 hr. From the results of this study, though the overall mean concentration (3.78 mcg/ml) was higher than the MIC (3.5 mcg/ml), most concentrations of streptomycin in the CSF were less than the mean MIC for M. tuberculosis which confirmed earlier evidence, indicating the poor penetration of the drug into the CSF (8,11,12). A complex molecular structure in addition to a high molecular weight of streptomycin may result in lower cerebrospinal fluid penetration even through inflamed meninges (77). However, if streptomycin is prescribed, it should be only at the initial phase of treatment, and perhaps it is

better to combine with pyrazinamide since they are said to be one - half bactericidal each and only together are considered to form a single bactericidal drug. (8,27,41,50).

There was no statistically significant correlation between CSF and serum concentrations of streptomycin ($p > 0.05$). Hence, the concentrations of the drug in CSF cannot be predicted from the serum concentrations.

II. Comparative Concentrations in CSF and Serum of Antituberculous Drugs between Patients with and without Concomitant Corticosteroids.

No comparative study on concentrations in CSF and serum of antituberculous drugs between patients with and without concomitant corticosteroids was previously performed. This is the first comparative study of the drugs. However, this study failed to show the difference in the mean concentrations of isoniazid as well as pyrazinamide, rifampin and streptomycin in CSF and serum at various intervals between these two groups ($p > 0.05$). Thus, the mean CSF/serum ratios of isoniazid, pyrazinamide, rifampin and streptomycin at various intervals between the two groups were not statistically significant different too ($p > 0.05$). The total means in CSF and serum, and the total CSF/serum ratios between two groups were not also significant different ($p > 0.05$) except that the total mean CSF concentration in group II (patients with concomitant corticosteroids) was higher than in group I (patients without corticosteroids) ($p < 0.01$). It seems that the concomitant corticosteroids did not affect the concentrations of the drugs in the CSF and serum. Isoniazid and pyrazinamide diffuse very well not only in the active state of tuberculous meningitis but also in normal meninges while rifampin

crosses the blood brain barrier adequately only when the inflammation is present and streptomycin is transported poorly to the brain. So, corticosteroids which was claimed to reduce the inflammation of the meninges would not decrease the levels of isoniazid and pyrazinamide in the CSF but might reduce the transport of rifampin and streptomycin (20). The results of this study agreed with the concept that corticosteroids did not affect the levels of isoniazid and pyrazinamide in the CSF. However, it failed to show that corticosteroids reduce the levels of rifampin and streptomycin. Thus, steroids can be used in Tuberculous meningitis whenever clinical signs and symptoms of the patients are suggested because they do not affect the CSF levels of the 4 antituberculous drugs.

III. Clinical Evaluation of Antituberculous Drugs in Tuberculous Meningitis Patients during Hospitalization

After the institution of these four antituberculous drugs in the patients, the evidence of clinical and CSF improvement were usually observed within 2 to 4 weeks. Fever gradually subsided and the patients regained consciousness with improvement of the neurologic signs. The CSF cell count decreased but not to normal levels at the end of hospitalization except in two patients (SM and PRT) in group I and one (YC) in group II whose CSF cell count had not decreased. The sugar concentrations in CSF also increased but not to normal levels at the same time. The elevation of the CSF protein persisted in most cases at the end of hospitalization. However, the clinical signs and symptoms of the patients improved at discharge from hospital.

The patients with most compatible to tuberculous meningitis were studied. The regimen for the treatment was systemic combination of isoniazid, pyrazinamide, rifampin and streptomycin. This regimen was also suggested as the most effective chemotherapy for the treatment of tuberculous meningitis by Forgan - Smith et al (8) as follows. At the initial phase of active inflammation, oral isoniazid and pyrazinamide, and intramuscular streptomycin should be given with or without oral rifampin in high dose, in view of the high sterilising activity of this combination. Treatment might then be continued with isoniazid and rifampin since streptomycin would no longer penetrate into the CSF and pyrazinamide, without an aminoglycoside antibiotic, is of low efficacy. In addition, Sifontes (27) recommended to use three or four antituberculous drugs including isoniazid, rifampin and others such as streptomycin, pyrazinamide and ethambutol in patients who harbor or are suspected of harboring isoniazid - resistant mycobacteria.

Studies of CSF drug levels are quite difficult because lumbar puncture has to be done. Since complications can be associated with lumbar puncture, it was done only when clinically indicated and should be performed by a specialized physician. The amount of CSF obtained from each lumbar puncture was also a problem as sometimes it was too small for determination of all 4 drugs. So, some data was missed out which was designated as blank in all of the tables shown.

Since there were only 16 patients included in this study and long-term follow up was not done, it is difficult to draw definite conclusion about the efficacy of this regimen and further studies should be carried out.