Reprinted from Indian Journal of Tuberculosis. Vol. XXVII, No. 2 (April 1980).

CHEMOTHERAPY OF TUBERCULOUS MENINGITIS WITH ISONIAZID PLUS RIFAMPICIN–INTERIM FINDINGS IN A TRIAL IN CHILDREN*

PADMA RAMACHANDRAN

Summary: Seventy six cases of tuberculous meningitis admitted to the Institute of Child Health and Hospital for Children, Madras were treated with a regimen of rifampicin, isoniazid and streptomycin daily for two months, followed by streptomycin twice a week plus ethambutol and isoniazid daily for 4 months. Treatment with isoniazid and ethambutol daily was continued for a further period of 6 months. In the earlier part of the study. isoniazid was prescribed in a dosage of 20 mg/kg. It was noted that about half of the children on isoniazid 20 mg/kg developed clinical jaundice with elevated levels of serum bilirubin and SGOT and SGPT levels. It was considered likely that the 'high dosage of isoniazid might have contributed to the high incidence ofjaundice and hence the dosage of the same was reduced to 12 mg/kg. With the reduced dosage of isoniazid, the incidence of jaundice was much lower, namely 20 %. 54 patients have so far completed the treatment period of 1 year. 13 of these died after admission to the study. The clinical and laboratory findings are presented.

Amongst all forms of tuberculosis, tuberculous meningitis still carries a high mortality and morbidity. This is due to the lack of established diagnostic criteria in the absence of bacteriological evidence and also because of the prolonged nature of therapy leading to irregular and incomplete treatment in the later months of chemotherapy.

The advent of the bactericidal drug rifampicin and the re-entry of pyrazinamide in the field of chemotherapy have dramatically changed the prospects of developing regimens which produce sterilisation of tuberculous lesions and have helped in reducing the duration of chemotherapy of pulmonary tuberculosis from the conventional 12-18 months to about 6 months. Rifampicin has been found to enhance the efficacy of regimens even when given only for the first two months The combination of rifampicin plus isoniazid has also been found to be highly effective in the treatment of tuberculosis of the spine in Madras patients. Information on the value of rifampicin in the chemotherapy of tuberculous meningitis is limited. The high efficacy of rifampicin-regimens in pulmonary tuberculosis and tuberculosis of the spine suggests that rifampicin-containing regimens would be of great value in the treatment of tuberculous meningitis. The interim findings of a study which is being undertaken to investigate the efficacy of a rifampicin-containing regimen in tuberculous meningitis in children in Madras are presented in this paper.

The study is being conducted by the Tuberculosis Research Centre of the Indian Council of Medical Research in collaboration with the Institute of Child Health and Hospital for Children, Madras, from where the patients are drawn.

Materials & Methods

76 cases of TB meningitis aged between 1 and 12 years who had not received more than two weeks of previous anti-tuberculosis treatment were admitted to the study.

Criteria for diagnosis:

Clinical : Presence of signs like fever, vomiting, irritability, apathy, refusal to play, anorexia and constipation in the early stages followed by well marked meningeal signs, mental confusion, neurological signs, coma and widespread paralysis.

CSF Changes :

Protein content more than 40 mgs %.

Sugar Content less than 50 mgs % .

Cells more than 10/cmm. predominantly lymphocytes.

Investigation

The following investigations were carried out :

1. *Mantoux test:* A 1 TU Mantoux test (PPD batch RT 23 with tween 80) on admission.

2. X-Ray Chest on admission and at the end of treatment.

3. Routine urine analysis and tests for acetyl isoniazid, bile salts, bile pigments and urobilinogen every month.

4. Estimations of SGOT, SGPT activity,

* Presented at the 34th Conference on Tuberculosis and Chest Diseases, Jaipur, 28-31, October. 1979.

** Tuberculosis Research Centre, Madras-600031.

serum bilirubin, blood Urea and Creatinine an admission, at 1 and 2 months and at the end of chemotherapy.

5. Estimation of haemoglobin, blood platelet count, total and differential white blood cell counts on admission, at 1 and 2 months and at the end of chemotherapy.

6. CSF examination for biochemical, cytological, smear and bacteriological examinations on admission and every two weeks thereafter.

Staging on admission :

At the time of admission patients were examined in detail with special reference to nervous system. They were classified into 3 stages (Table I) according to the British Medical

Table 1

Staging on Admission

Stage	Patients	
	No.	%
I	9	12
II	62	82
III	5	6
Total	76	100

Research Council (1948) classification. Cases were divided into :

Stage I : Patients were fully conscious and rational with signs of meningeal irritation but with no focal neurological signs or signs of hydrocephalus.

Stage II: Patients were mentally confused and/or had such neurological signs as squints or hemiparesis.

Stage III : Patients were mentally inaccessible owing to the depth of stupor or delirium on admission and/or had a complete hemiplegia or paraplegia.

Treatment Schedules:

All patients were treated for a period of 12 months. During the first 2 months, the patients were treated with 3 drugs-streptomycin, isoniazid and rifampicin daily (Table 2). During 3-6 months, they received ethambutol plus isoniazid daily, supplemented by streptomycin administered twice a week. During the last 6 months, they were treated with ethambutol plus isoniazid daily.

Table 2

Drug Regimens

Month	Drugs
0-2	Streptomycin, isoniazid and rifampicin daily.
3-6	Ethambutol and isoniazid daily plus streptomycin twice-weekly.
7-12	Ethambutol and isoniazid daily.

Streptomycin was employed in a dosage of 40 mg/kg body-weight, rifampicin 12 mg/kg daily and ethambutol 17.5 mg/kg daily (Table-3). The first 26 patients were treated with isoniazid in a daily dosage of 20 mg/kg, a dosage commonly used by most Indian paediatricians for the treatment of tuberculous meningitis. However, a large number of them developed clinical jaundice during the initial phase of treatment with isoniazid and rifampicin. It was considered likely that the high dosage of isoniazid might have contributed to the high incidence of hepato-toxicity. Patients admitted to the study subsequently were all treated with a lower dose namely, 12 mg/kg isoniazid.

Table 3

Drugs and dosages

Streptomycin	40 mg/kg.
Rifampicin	12 mg/kg.
Ethambutol	17.5 mg/kg.
Isoniazid	20 mg/kg (26 pts.) 12 mg/kg (50 pts)

Results

Characteristics on admission:

All the patients in the study were under 7 years of age, and 88% were aged 4 years or less (Table 4).

Table 4

Age distribution

Age (years)	Patients	
1	26	34%
2	15	20%
3	11	14%
4	15	20%
5	5	7%
6	4	5%
7–12	0	0
Total	76	

Table 5

Mantoux results

Induration (mm)	Patients	
0	26	34%
1-4	10	13%
5-9	3	4%
10-14	13	17%
15-19	16	21%
20-29	7	9%
N.A.	1	1%
Total	76	

Tuberculin test was positive with indurations of 10 mm or more in about half of the patients (Table 5). The remaining patients had reactions of less than 10 mm(including a third (34%) who had a reaction of '0' mm. Cerebrospinal fluid was positive for Mycobacterium tuberculosis in 30% of the cases (Table 6). Thirty four (45%) patients had a history of contact with pulmonary tuberculosis and 38 (50%) had an abnormal chest X-ray suggestive of pulmonary tuberculosis.

Table 6

Bacteriological findings on admission

Stage	*Patients*		*Culture Positive*
I	9	12%	4
II	62	82%	18
III	5	6%	1
Total	76		23 (30%)

Clinical Progress :

Of the 76 patients, 54 have completed 1 year of treatment. Of these, 13 (24%) patients died after admission to the study, 20 (37%) patients made a complete recovery and the remaining 21 (39%) patients also recovered but had been left with residual damage, which was considered to be severe in 15% and mild to moderate in 24% (Table 7). Mild residual damage implied such sequelae as hyperactivity, irritability, mild perceptual defects and slight motor impairment like facial paresis or monoparesis. Moderate residual damage included such defects as hemiparesis, involuntary movements and mental dullness. Severely damaged children usually remained unconscious or if consciousness was regained they were incapable of independent life.

Hepatotoxicity:

As pointed out earlier the first 26 cases were given isoniazid in a dosage of 20 mg/kg daily. Four cases died before completing the rifampicin therapy (Table 8) ; they did not have hepatic toxicity and are excluded from the analysis. Out of the remaining 22 cases, 11 (50%) developed clinical jaundice with elevated serum bilirubin levels and a significant rise in the SGOT and SGPT levels. The treatment in these cases was suitably modified.

Table 7

Status at 1 year

Stage	No. of patients	Deaths	Residual damage		Complete recovery
			Severe	Mod/Mild	
I	7	0	1	0	6
II	45	11	7	13	14
III	2	2	0	0	0
All	54	13 (24%)	8 (15%)	13 (24%)	20 (37%)

Table 8

Incidence of Jaundice in the first two months

	High Dose INH 20 mg/kg	Low Dose INH 12 mg/kg
No. of patients	26	50
Deaths	4	10
No. in analysis	22	40
Developed Jaundice	11 (50%)	8 (20 %)

It was considered likely that the high dosage of isoniazid (20 mg/kg) when given in combination with rifampicin may have contributed to the high incidence of jaundice. The daily dosage of isoniazid was, therefore, reduced to 12 mg/kg in the subsequent part of the study. Fifty patients were treated with the regimen containing the lower dosage of isoniazid. Ten patients died before completing the two months of treatment and none of them had hepatic toxicity. Out of the remaining 40 cases, 8 developed jaundice with elevated bilirubin, SGOT and SGPT levels. Thus there was a reduction in the incidence of jaundice following reduction of the dosage of isoniazid, but the incidence is still high. This suggests that the use of a combination of isoniazid plus rifampicin entails a high risk of hepatotoxicity in children with tuberculous meningitis.

Conclusions

In conclusion, the combination of isoniazid 20 mg/kg plus rifampicin administered daily, was associated with high and unacceptable levels of hepatotoxicity in children with tuberculous meningitis; the incidence was substantially lower in children treated with a lower dosage of isoniazid, namely 12 mg/kg, plus rifampicin. The results of chemotherapy with a regimen of isoniazid plus rifampicin daily for 2 months, followed by ethambutol plus isoniazid daily for 10 months, supplemented with streptomycin during the first 6 months were highly encouraging. Thus, as many as 76% of the patients had survived at the end of one year, a gratifying finding considering that over 80% of the patients belonged to stage II or stage III on admission.