Paediatrica Indonesiana 19 : 285 — 294. Nov. — Dec. 1979.

ORIGINAL ARTICLE

The Treatment of Tuberculous Meningitis in Children with A Combination of Isoniazid, Rifampicin and Streptomycin (A preliminary report)

by

NASTITI N. RAHAJOE, NOENOENG RAHAJOE*, I. BOEDIMAN*, MARDJANIS SAID* and S. LAZUARDI***

(Department of Child Health and Department of Neurology**, Medical School, University of Indonesia, Jakarta)*

Abstract

Twenty-two cases of tuberculous meningitis have been treated with isoniazid, streptomycin and rifampicin and 19 cases with isoniazid, P.A.S. and streptomycin. Both groups received corticosteroid at the beginning of the treatment. The 2 groups were compared on the clinical and neurological improvement, duration of necessary hospitalization, the presence of sequelae, and the death rate. Also the tolerability of both regimens was compared.

It seemed that rifampicin shortened the necessary hospital stay. It was also found that sequelae were less in the rifampicin group than in the standard regimen group.

There was no obvious difference in the mortality rate of both groups which might be due to the fact that the cases were of the advanced stage. Anticonvulsants might influence the high incidence of liver dysfunction as could be seen in the high incidence of jaundice in the rifampicin group.

The cases are still being followed up for 18 months or more to obtain a final conclusion.

Received 19th. April 1979.

Introduction

The incidence of tuberculous meningitis and other complications of primary tuberculosis is still high in the Department of Child Health, Medical School, University of Indonesia, Dr. Cipto Mangunkusumo General Hospital, Jakarta. During the years 1970 to 1977, 87 — 147 children each year were hospitalized with tuberculous meningitis, whereas the total admission in the hospital were 4788 — 5383 children each year.

For the treatment of tuberculous meningitis, the standard regimen of tuberculosis with Isoniazid, PAS and/or Ethambutol and Streptomycin, and also corticosteroid is still used. With this regimen, the death rate was 35%, and 90% of the patients recovered were with sequalae.

The aim of this study is to compare the efficacy of a combination of Isoniazid, Streptomycin and Rifampicin in the treatment of tuberculous meningitis, with that of the standard regimen.

Material and method

New patients under the age of 12 years with tuberculous meningitis hospitalized during the years 1977 — 1978 were divided into 2 groups by random method.

Group I or the Rifampicin Group received Isoniazid daily with a dosage of 20 mg per kg body weight divided into 2 or 3 doses for at least 18 months, Streptomycin 30 - 50 mg per kg body weight daily for 1 month and Rifampicin (Rimactane syrup, Ciba, 20 mg Rifampicin per ml syrup) 10 - 15 mg per kg body weight daily as a single dose in an empty stomach for 6 months.

Group II or the Standard Regimen Group received Isoniazid 20 mg per kg body weight daily in 2 - 3 divided doses for at least 18 months, PAS 200 - 300 mg per kg body weight daily in 2 - 3 divided doses for at least 12 months, and Streptomycin 30 - 50 mg per kg body weight daily for 3 months which may be continued 3 times weekly for other 3 months. Both groups received corticosteroid at the beginning of treatment; corticosteroid was administered intramuscularly for the first 3 days and then continued by oral prednisone 1 - 3 mg per kg body weight daily in 3 divided doses for about 4 weeks, then tapering off slowly and stopping at the end of the twelfth week. Sometimes anticonvulsants such as phenobarbital and diphenylhydantoin might also be administered at the beginning of treatment to control convulsions. Diazepam might be given to those with severe spasticity.

The diagnosis of tuberculous meningitis was based on :

1. Physical examination on the general condition, convulsion, signs of meningeal irritation and other neurological manifestation;
2. Lumbar puncture : a clear or xanthochromic fuid, a rise in the cell count usually lymphocytes predominate, low content of glucose and the protein is invariably increased, and also 1 or more of the followings;

3. Positive tuberculin test;
4. Chest X-ray abnormality;
5. Tubercle bacilli findings in the cerebrospinal fluid and/or the gastric lavage;
6. History of contact.

Before treatment were also noted the appetite, body weight, liver function test, serum glutamic oxalo acetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and routine examinations of the peripheral blood, urine and feces. These examinations were repeated after 2 weeks, 1 month, and then every month for 6 months. It was planned to follow up the patients for 2 years or more.

The 2 groups were compared on :

1. the clinical and neurological improvement,
2. duration of necessary hospitalization,
3. the presence of sequelae, and
4. the death rate.

Also the tolerability of both regimens was compared.

All the patients were hospitalized for at least 12 weeks for close observation. The patients were also divided into 3 stages according to the Medical Research Council of Great Brittain to compare the prognosis.

Stage I : the patient is fully conscious and rational, with signs of meningeal iritation but no focal neurological signs or signs of hydrocephalus.

Stage II : the patient is mentally confused and/or has focal neurological signs such as extraocular paralysis or hemiparesis.

Stage III : the patient is unresponsive or inaccessible due to stupor or delirium and/or has complete hemiplegia or paraplegia.

Results

Forty-one cases of 5 months to 12 years were included in this report.

Twenty two cases were included in group I, and 19 in group II. Most of the cases were under 6 years (see table 1).

TABLE 1 : *Age and sex distribution*

Age (year)	Rifampicin group (I)		Standard regimen group (II)	
	Male	Female	Male	Female
Under 1	2	2	4	0
1 —	3	3	3	2
2 —	4	4	4	1
4 —	1	1	1	1
6 — 12	2	0	2	1
Total	12	10	14	5
	22		19	

As can be seen in table 2, out of 22 cases of group 1, 18 cases were undernourished, and 4 cases were of normal body weight; whereas out of 19 cases of group 2, 16 cases were undernourished and 3 cases were of normal body weight. The grouping of the nutritional condition was done using percentile 50 of the Harvard standard for body weight, and the clinical signs of undernutrition.

TABLE 2 : *Nutritional condition*

Age (year)	Rifampicin group				Standard regimen group			
	P. 50	80% — P. 50	60-80% P. 50	< 60% P. 50	P. 50	80% — P. 50	60-80% P. 50	< 60% P. 50
0 —	0	2	2	0	1	1	1	1
1 —	0	0	4	2	0	0	5	0
2 —	0	0	3	3	0	0	2	3
4 —	0	2	2	1	0	1	0	1
6 — 12	0	0	1	0	0	0	2	1
Total	0	4	12	6	1	2	10	6
	4		18		3		16	

The nutritional conditions in the 2 groups were about the same.

None of the cases were of the first stage of tuberculous meningitis as seen in table 3. Eight cases of the Rifampicin group were of stage II, and 13 cases stage III.

TABLE 3 : *Distribution of cases in groups I & II by stages of tuberculous meningitis*

Stage	Rifampicin group (I)	Standard regimen group (II)
I	0	0
II	8	6
III	14	13
Total	22	19

Mantoux test using PPD-RT23 2 TU was done in all cases; 20 out of 22 cases of the Rifampicin group gave positive results and 2 cases gave negative results both of stage III. Fourteen cases of the Standard Regimen group gave positive results, and 5 gave negative results, these 5 cases were also of stage III.

TABLE 4 : *Radiological picture of the lung*

Radiological picture of the lung	Rifampicin group	Standard regimen group
Miliary spread	6	7
Primary infiltrate	5	5*
Massive infiltration	9	4
Minimal changes	1	0
Bronchopneumonia	1	2
Consolidation	0	1

* 1 case with calification.

Table 4 shows the radiological picture of the lungs found in the 2 groups. Six cases of group I and 7 cases of group II showed miliary spread in the rontgenogram of the lungs.

In the Standard Regimen group there was 1 with spondylitis, 1 with coxitis, and 1 with Scrofuloderma.

BCG scar was found in 2 out of group I and 3 out of group II.

Six cases (27.2%) of group I died during hospitalization, 1 case died before 1 week, 2 cases within 1 - 2 weeks, and 3 cases within 2 - 4 weeks; these 6 cases were all of stage III. Out of 19 cases of group II, 5 cases (26.3%) died during hospitalization, 2 cases before 1 week, 2 cases within 1 - 2 weeks, and 1 case within 2 - 4 weeks of hospitalization. One of these 5 cases was stage II with miliary tuberculosis, and the other 4 were of stage III.

Seven cases of group I recovered with sequelae, 5 cases with spastic tetraparesis and mental retardation, 1 case with spastic tetraparesis, mental retardation and ptosis, and 1 case with hemiparesis.

Nine cases of group I recovered without any sequelae. Folow-up studies are still being done to see further mental and motoric development.

Eleven cases of group II recovered with sequelae, 4 cases with spastic tetraparesis and mental retardation, 2 cases with spastic tetraparesis, mental retardation and hydrocephalus, 1 case with spastic tetraparesis, mental retardation and hydrocephalus, 1 case with spastic tetraparesis, mental retardation and strasbismus, 1 case with strasbismus, 2 case with hemiparesis, and 1 case with recurrent headache and edema of the optic nerve papilla (papilledema). Also in group II further follow up is still being done.

Those 7 cases of group I with sequelae were all stage III, whereas those 11 cases of group II with sequelae, 2 cases were of stage II and 9 cases of stage III.

The cases were stated as recovered when there were no more signs of meningeal irritation and the cerebrospinal fluid was normal. After two weeks of treatment 6 cases (27.3%) recovered, 3 cases died, and 1 case of group I detericrated clinically and neurologically with severe jaundice. Out of group II, 4 cases recovered after 2 weeks of treatment (21%) and 4 cases died.

After 1 month 5 more cases recovered so that there were 11 cases (50%) of group I who recovered, and another 3 cases died; whereas in group II 3 more cases recovered so that 7 cases (36.8%) recovered after 1 month and 1 more case died.

After two months of treatment 14 cases (63.6%) og group I recovered and 10 cases (52.6%) of group II recovered.

After 3 months of treatment 1 out of 14 cases of group I that had recovered after 2 months became active again; this was due to the discontinuation of Rifampicin as severe jaundice develo-

ped, but there were other 2 cases which recovered so that 15 cases (68.1%) recovered by the end of the third month. Twelve cases (63.1%) out of group II recovered after 3 months of treatment.

At the end of the fourth month there was no change of the number of cases that recovered out of group I, whereas out of group II 13 cases (68.4%) recovered.

After 5 months all cases of group I, which were still alive, recovered, i.e. 16 cases (72.7%) and group II 13 cases (68.4%). One case of group II recovered after 5 months of treatment and refused further hospitalization (see diagram).

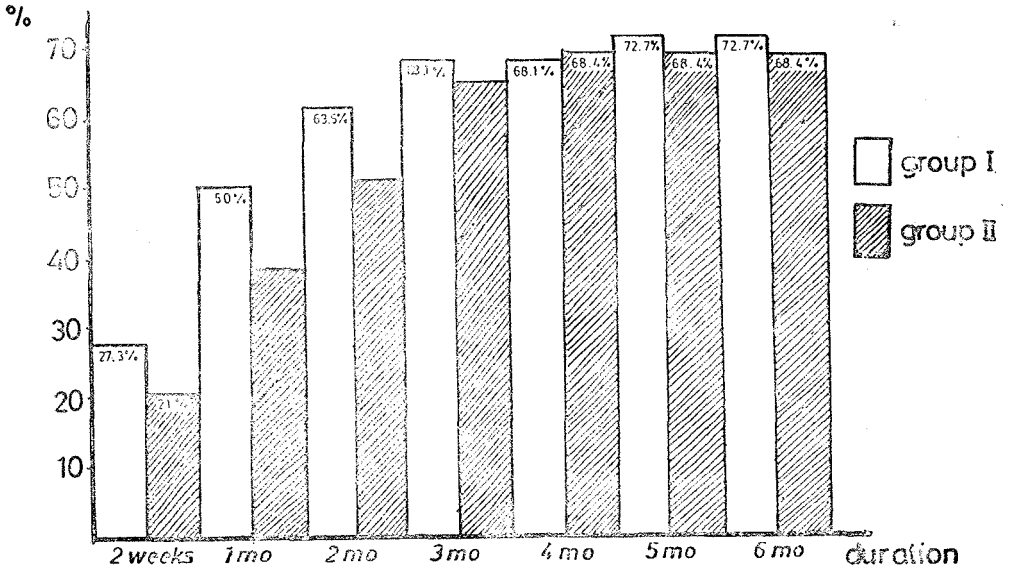

DIAGRAM 1 : *Cummulative number of cases recovered.*

After recovery from tuberculous meningitis, 3 more cases of group I died due to other causes, 1 with gastroenteritis and dehydration, and 2 died at home due to unknown cause, as the parents reported the deaths without bringing the children. And in group II also 3 more cases died after recovery from tuberculous meningitis, 1 due to aspiration pneumonia, 1 with measles and bronchopneumonia, and 1 died at home because of unknown cause.

Six cases of group I developed jaundice after 9 - 33 days of treatment. Four cases recovered from jaundice after reducing the dosage or stopping isoniazid and/or rifampicin, and jaundice did not recur when full dosage of the drugs was given again; only 1 case of these 4 cases showed jaundice again after redu

cing isoniazid only. One case died with severe jaundice after 3 weeks of treatment. Another case with severe jaundice and clinical deterioration, and attempt to reduce by decreasing the dosage of isoniazid failed so that rifampicin was stopped, which was followed by a gradual decrease of bilirubin and became normal after 2 weeks.

One case group II developed jaundice after 40 days of treatment, but after stopping diphenylhydantoin jaundice disappeared within 12 days. Blood test for hepatitis B was performed in all cases with jaundice except in 1 case who died with severe jaundice, and the results were all negative. Liver biopsy was also done except in 1 case with unspecific results.

The development of jaundice in this trial has been reported separately. Tubercle bacilli were found in only 2 cases of group I and in 2 cases of group II on the culture of the cerebrospinal fluid.

The sensitivity test showed that the tubercle bacilli were still sensitive to all anti-tuberculosis drugs used.

BCG scar found in 2 cases of group I and in 3 cases of group II.

Discussion

It is found that most of the cases in this clinical trial were of severe stage with poor nutritional condition in both groups.

More than 90% of the cases were under 6 year old. No difference was found on the chest X-ray findings in both groups.

The death rate in the Rifampicin Group 26.3% which showed that there was no significant difference between both groups, except that death also happened in 1 case of stage II of the Standard Regimen Group, whereas of the Rifampicin Group all were of stage III.

Sequelae were found in 7 cases (43.5%) of the survived cases of the Rifampicin Group and in 11 cases (78.6%) of the Standard Regimen Group. This seems to show a significant difference between the 2 groups. It should be remembered that most of the cases in the 2 groups were of stage III or severe so that the high incidence of sequelae could not be avoided.

After one month of treatment 11 cases (50%) of the Rifampicin Group improved, whereas only 7 cases (36.8%) of the Standard Regimen Group improved. This may show the difference of necessary hospital stay in the 2 group. Campos et al., (1970) found good results in the treatment of tuberculous meningitis using isoniazid, ethambutol, rifampicin and corticosteroid, compared to those receiving isoniazid, P.A.S., streptomycin and corticosteroid. Visudhiphan and Chiemchanya (1975) also found that rifampicin reduced the mortality and morbidity and shortened the duration of hospital stay.

The incidence of jaundice was relatively high in the Rifampicin Group. Six cases of the Rifampicin Group developed jaundice after 9 - 33 days of treatment, and only 1 case did so in the Standard Regimen Group.

After the discontinuation of diphenylhydantion in that 1 case of the Standard Regimen Group the jaundice disappeared. Kutt et al. (1966) studied cases with signs of diphenylhydantoin intoxication when the drug was taken together with isoniazid; this was caused by the depression of parahydroxylation of diphenylhydantoin by isoniazid resulting in diphenylhydantoin intoxication.

Lowering the dosage of isoniazid as recommended by Dieu (1972) was only successful in 1 case of the Rifampicin Group in which jaundice disappeared after 2 weeks. In the other cases, rifampicin had to be stopped to control jaundice. Hepatitis B antigen was negative in 6 cases examined. Liver biopsy done on 6 cases revealing unspecific changes indistinguishable to those of viral hepatitis.

Rahajoe et al. (1976) observed jaundice only in 1 out of 64 cases with pulmonary tuberculosis treated with isoniazid and rifampicin. Jaundice disappeared after stopping the treatmen and did not reappear after reconstitution of the same treatment.

The higher incidence of jaundice in this series may be influenced by the use of phenobarbital, diphenylhydantoin or diazepam in tuberculous meningitis. The possibility of the meningitis itself to influence the incidence of jaundice is not clear yet.

Visudhipham and Chiemchanya (1975) observed that one third of the cases had a transient elevation of the transaminases and bilirubin, and after reducing the dosage of rifampicin the values became normal again. Campos et al. (1970) did not mention the incidence of jaundice in their series.

Smith (1954) and Rahajoe et al. (1976) observed that SGOT and SGPT were elevated after 4 - 8 weeks' treatment of tuberculosis with the standard regimen as well as rifampicin, and then decreased slowly without reducing or stopping the anti-tuberculosis drugs.

Acknowledgement

The authors express their gratitude to P.T. Ciba-Geigy Pharma Indonesia for the supply of the drugs and expenses necessary in this study.

REFERENCES

1. CAMPOS, L.D., FONTOURA, E. and DUARTE, G.: The present treatment schedule of tuberculous meningitis in the Pavilhae Infantil Roberto Rangel Lima, in conjunction with Sanatorial Rafael de Paula Souza. XVth National Congress on Tuberculosis, Curitiba-Parana, 1970.
2. DIEU, J.Cl.: Role de l'Isoniazide dans l'hepattotoxite de l'association INH = Rifampicine dans la tuberculose de l'enfant. J. Med. Lyon 53 - 1323 (1972).

3. KUTT, H., WINTERS, W. and Mc DOWEL, F.H.: Depression of Parahydroxylation of Diphenylhydantion by Antituberculosis Therapy. Neurology (Minneap.) 16 : 594 (1966).

4. RAHAJOE, N.N., SUTOTO, RAHAJOE, N., BOEDIMAN, I. and SUTEJO: Rifampicin in combination with isoniazid in the treatment of childhood tuberculosis. Paediatr. Indones. 16 : 544 (1976).

5. SASTROASMORO, S., RAHAJOE, N., RAHAJOE, N.N., BOEDIMAN, I. and SAID, M.: Isoniazid-rifampicin associated hepatitis. IVth Nat. Congr. Indones. Pediatr., Yogyakarta, 1978.

6. THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN (as cited by Gilroy. J. and Meyer, J.S. in Medical Neurology. pp. 364 - 367 (Macmillian, Toronto 1969).

7. VISUDHIPHAN P. and CHIEMCHANYA, S.: Evaluation of rifampicin in the treatment of tuberculous meningitis in children. J. Pediatr. 87 : 983 (1975).