
ORIGINAL ARTICLE

Treatment of Neonatal Purulent Meningitis with a Sulphamethoxazole (SMZ)/Trimethoprim (TMP) Combination

by

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Abstract

This paper describes our experience in treating neonatal meningitis with an intravenous Sulphamethoxazole/Trimethoprim (SMZ-TMP) combination.

Fifteen neonates ranging in age from 6 to 36 days were included in this study. Cerebrospinal fluid isolates were as follows :

S. havana (3), S. oranienburg (2) and haemolytic streptococci (1), the remaining 9 cultures were negative. Those bacteria isolated were all sensitive to SMZ/TMP. A solution of SMZ 80 mg/ml and TMP 16 mg/ml in 40% propylene glycol was used with a daily dose of 10 mg/kg B.W. TMP for the first 3 days followed by 6 mg/kg B.W. TMP for 18 days or longer, divided in two dose given intravenously every 12 hours.

Thirteen patients recovered, but two died of neurological complications, one with ventriculitis and the other with a subdural empyema.

No hematological or cutaneous or gastrointestinal side effects were observed. The liver and renal function tests performed on 5 out of the 15 patients on the first few days of hospitalization and 3 weeks later were all within normal limits. The use of parenteral SMZ-TMP in neonatal meningitis showed an encouraging result considering the fact that our previous mortality rate was 60%.

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Introduction

Despite the use of newer antibiotics the prognosis of neonatal meningitis remains poor. During the past two decades there has been no change in the case fatality rate and in the percentage of survivors with mental impairment and neurologic sequelae (McCracken, 1977).

In our department since 1975 the average case fatality rate of neonatal purulent meningitis has been 60%.

The combination of sulphamethoxazole (SMZ) and Trimethoprim (TMP) acts synergistically both in vitro and in vivo and has a broad spectrum antibacterial effect. It proved to be effective in the therapy of a variety of infections including cases of purulent meningitis in the pediatric age group (Morizaria et al., 1969; Sabel and Brandberg, 1975).

However there has been limited reported experience with this combination in the first month of life. The purpose of this study was to determine whether a combination of SMZ-TMP would be effective in the treatment of neonates with purulent meningitis.

Material and Methods

Fifteen neonates diagnosed as having purulent meningitis hospitalized at the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta from May 1977 to November 1978 were included in this study. The criteria used to make the clinical diagnosis included a positive spinal fluid culture, polymorphonuclear

pleocytosis of spinal fluid and decreased spinal fluid sugar content.

Spinal fluid pleocytosis and hypoglycorrhachia with an appropriate clinical course was used if the culture was negative. Low birth weight infants with purulent meningitis were not included in the study.

A solution of SMZ 80 mg/ml and TMP 16 mg/ml in 40% propylene glycol (BACTRIM, Hoffmann-La Roche AG, Basle Switzerland) was diluted with 20 volumes of 5% glucose and given intravenously slowly for about one hour. The daily dose was 10 mg TMP/kg body weight for the first 3 days followed by 6 mg/kg body weight TMP for 18 days or longer divided into two doses every 12 hours.

Several criteria were used to evaluate clinical improvement including the disappearance of fever and irritability, the emergence of the sucking reflex, improvement in the level of consciousness, improvement of neurologic status, and weight gain.

The following standard laboratory controls were performed: a blood count to include hemoglobin, red cells, reticulocytes, total and differential white blood count and a urinalysis for protein, glucose, red and white cells.

These were done once a week during treatment. S.G.O.T., S.G.P.T., urea clearance and creatinine clearance examinations were performed before and after treatment. Close observation for unexpected side-effects was carried out during treatment.

Results

Fifteen neonates ranging in age from 6 to 36 days were included in this study. They comprised 18,8% of the 80 cases of purulent meningitis seen in children during the same period of time out of approximately 5500 admissions.

The base line data for the neonates on admission was as follows: Nine of the 15 infants were male and 6 were female.

One patient was 6 days old on admission, nine were 7 — 15 days old, four were 16 — 30 days and one was 36 days old.

Poor weight gain was observed in 2 cases. Gram-negative rods were isolated from the CSF or blood of 6 neonates; *S. havana* (3), *S. oranienburg* (2) and haemolytic streptococci (1) from the CSF and *E. coli* (1) from the blood.

The remaining 9 cultures from the CSF were negative. The bacteria isolated were all sensitive to the SMZ-TMP combination. Two cases were delivered at home, and helped by traditional birth attendants.

Five cases were delivered at clinics, five helped by midwives and 3 by doctors.

Predisposing perinatal factors were that two mothers had unexplained fever during the perinatal period and one mother had an unexplained post partum fever.

Premature rupture of the amniotic membranes occurred in 2 instances.

The diagnosis of purulent meningitis was made in 2 cases after lumbar puncture was performed since these patients were diagnosed as having sepsis on admi-

ssion. Two infants were asphyxiated at birth with Apgar scores at one minute of 6 or less. One patient had a difficult delivery with a breech presentation. Feeding difficulties, either refusal of food or vomiting, were the most common presenting symptoms in our series.

Convulsions occurred in 8 out of the 15 infants. An impairment of the infants' reactions to stimuli and particularly irritability was frequently observed. These were mostly of short duration lasting 24 hours or less and were followed by lethargy. Cyanosis was observed in 4 cases.

Fever and diarrhoea were observed in four and two infants respectively. The neurological findings on admission included convulsions in 8 patients, opisthotonus in 5 and a bulging fontanelle in 4 cases.

The criteria for clinical improvement were as follows:

- (1) Disappearance of symptoms (fever and hyperirritability), return of level of consciousness to normal, the emergence of the sucking reflex and the improvement of other neurologic findings, less than 10 days after treatment;
- (2) within 10 — 19 days onset of treatment;
- (3) more than 20 days after SMZ-TMP administration has begun.

Results of treatment based on clinical findings are shown in table 1. The laboratory findings after treatment showed improvement of cerebrospinal fluid cell counts and sugar value within 21 days of treatment in 10 and 12 cases respectively and improvement after more than 21 days of treatment in 4 cases.

Complications and outcome in the patients are shown in table 2.

Seven out of thirteen patients were followed up for 1 — 2 years and 5 children showed normal motor and mental development while 2 others exhibited signs of mental retardation.

Side-effects :

No cutaneous or gastrointestinal side effects were observed. Hemoglobin : three patients had a drop of Hb from 15 — 16 g/100 ml to 11,3 — 12,8 g/100 ml which is not unusual during a severe infection. Following SMZ-TMP therapy a rise of Hb was seen in these patients.

No thrombocytopenia or leucopenia were observed. Urinalysis for protein, glucose, red and white cells which were done weekly were all within normal limits.

Urea clearance, creatinine clearance, SGOT and SGPT were performed in 5 out of the 15 cases, on the first few days of admission and 3 weeks later. The results are shown in table 3.

Discussion

Neonatal purulent meningitis is regarded as a problem of particular importance because of the difficulty in early diagnosis, the high mortality as well as serious sequelae. (McCracken and Shinefield, 1966; Berman and Banker, 1966).

The diagnosis of bacterial meningitis should be confirmed by a positive smear, culture and findings in the spinal fluid. However, in the neonatal period one must evaluate the laboratory findings

carefully since the normal values for cerebrospinal fluid in newborns resemble pathologic values in older infants and adults.

The normal cerebrospinal fluid of newborn infants is often xanthochromic, pleocytotic and has a high protein content.

These findings are more pronounced in low birth weight infants. (Bouer et al., 1965; Monintja et al., 1971).

Normal newborns can also have increased spinal fluid protein up to a level of 200 mg % (Monintja et al., 1971).

Therefore a diagnosis of purulent meningitis was accepted for the culture-negative group in our series if there was a mild decrease in glucose content. A positive culture from the spinal fluid in our series was 40%, a figure which might have been affected by the delay between when the specimen was obtained and when it was put on the culture media, and whether antibiotic had been given before the culture was taken (Dyggve, 1962). The CSF culture was also negative in 2 cases who had a positive blood culture and whose spinal fluid revealed a pleocytosis and hypoglycorrachia.

Premature rupture of the amniotic membranes and maternal infections were the most significant associated maternal factors, whereas the most common associated infant factors in our series were infection (septicemia, funiculitis) and asphyxia at birth.

The symptoms and signs described by several authors (Chevrie and Aicardi, 1969; Lewis and Gupta, 1977) of feeding difficulties, convulsions, lethargy, cyano-

sis and fever, were also the most common symptoms in our series.

Of the 8 infants with convulsions the meningitis was suspected at the time of presentation but in the remaining 7 cases the presenting symptoms and signs were non specific and a lumbar puncture was performed. A rapid recovery was seen in most cases after therapy with SMZ-TMP.

In two of the fatal cases (13,3%) the cause of death was directly attributed to the meningitis. One patient died of ventriculitis after 7 days of treatment. In this case, however, a ventricular tap was probably performed too late. A second patient died of a subdural empyema after 6 days of treatment.

There is still controversy about the definition of the neonatal period, but in accordance with the recommendation of the World Health Organization most authors (Smith et al., 1956; Watson, 1957) use 28 days.

Some authors, however, use one month, while others use two months in their reports. During the neonatal period (i.e. less than 8 weeks) group B streptococci and *E. coli* are the most common cause of meningitis (McCracken, 1976). In this study the most frequent isolation was *Salmonella* spp.

The treatment of purulent neonatal meningitis has been Penicillin G or Ampicillin in combination with one of the aminoglycosides (Overturf and Wehrle, 1979).

Several authors have reported the tendency for an increase in resistance, espe-

cially of the Gram-negative bacilli against ampicillin (Lindberg et al., 1977).

Gentamicin is now considered the drug of choice but has a low penetration through the blood-brain barrier (Sabel and Brandberg, 1975). SMZ-TMP is more effective due to its good penetration into the CSF. The concentration in serum one hour after injection by the intravenous route is fairly high with a mean of 100 ug/ml.

The mean value in the CSF is about a third of that in the serum (Sabel and Brandberg, 1975). In a survey of the susceptibility to Ampicillin of 150 *E. coli* strains isolated from cultures, only 17% were fully susceptible and 51% relatively susceptible compared to 81% for SMZ-TMP combination (Sabel and Brandberg, 1975). There are few published results on the use of parenteral SMZ-TMP in infants and experience with side effects in this age-group is limited. Boudierlique (1980) treated 23 neonates and infants with septicemia, 4 of whom had meningitis. Sixteen patients were less than 18 days old.

Treatment failed in only 2 cases and no serious side effects were observed. None developed kernicterus. Due to the wellknown fact that sulphonamides may displace bilirubin from albumin binding sites therefore increasing the risk of toxic effects on the CNS in an icteric infant, treatment with sulphonamides during the first week of life and especially of icteric or very immature infants is not advised (Odell, 1959; Sabel and Brandberg, 1975).

The study by Boudierlique using parenteral SMZ-TMP in neonates and this pilot

study gave encouraging results with no serious side effects from the SMZ-TMP combination. A randomized comparative trial of SMZ-TMP against ampicillin with gentamicin has now been initiated.

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TABLE 1: Results of treatment of neonatal purulent meningitis patients

| Clinical criteria | No. of patients responding by day of treatment | | |
|--|--|-------|------|
| | < 10 | 10-19 | ≥ 20 |
| Disappearance of fever | 4 | — | — |
| Disappearance of hyperirritability | 4 | 1 | — |
| The child became alert | 8 | 5 | 2 |
| The emergence of the sucking reflex | 10 | 5 | — |
| Improvement of other neurologic findings | 7 | 4 | 4 |

TABLE 2: Complications and outcome in neonatal purulent meningitis patients.

| Complications | Died | Survived | Total |
|------------------|------|----------|-------|
| Ventriculitis | 1 | — | 1 |
| Subdural empyema | 1 | 1 | 2 |
| Hydrocephalus | — | 1 | 1 |
| Spasticity | — | 3 | 3 |

TABLE 3: Results of the renal and liver function tests in 5 neonatal purulent meningitis patients.

| Case No. | Urea clearance ml/min/1,73 m ² | | Creatinine clearance ml/min/1,73 m ² | | SGOT IU | | SGPT IU | |
|----------|---|-------|---|------|---------|------|---------|------|
| | I * | II ** | I | II | I | II | I | II |
| 2 | 20.8 | 29.8 | 23.4 | 36.8 | 13 | 14.6 | 14 | 15.8 |
| 10 | 27.6 | 27.8 | 36.2 | 45.8 | 15.8 | 22.6 | 20.8 | 24.6 |
| 11 | 28.6 | 34.8 | 38.8 | 48.8 | 18.6 | 20.8 | 22.4 | 28.8 |
| 12 | 35.2 | 37.5 | 44.8 | 54.2 | 20.8 | 29.8 | 24.2 | 28.8 |
| 15 | 23.6 | 28.8 | 24.6 | 30.2 | 14.6 | 18.8 | 12.4 | 19.4 |

* Within the first few days of admission

** Three weeks later