ORIGINAL ARTICLE

Experience with Sulphamethoxazole (SMZ)/Trimethoprim (TMP) combination in Purulent Meningitis not Responding to Conventional Microbial Therapy

by

SUMARMO; MUGIYO K.; MANDOYONO; LAURITHA S.P. and ADJI SUNTORO

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

Abstract

Ten infants ranging in age from two days to nine months with purulent meningitis who were considered therapeutic failures after conventional microbial therapy (i.e. ampicillin, chloramphenicol, gentamicin, amikin, cloxacillin in any combination) were included in this study. A solution consisting of SMZ 80 mg/ml and TMP 16 mg/ml in propylene glycol (Bactrim, Hoffman-La Roche A.G. Basle/Switzerland) was given intravenously to the patients. The daily dose was 10 mg/kg BW TMP/24 hours for the first three days followed by 6 mg/kg BW TMP/24 hours divided in two doses given intravenously every 12 hours.

Nine patients recovered, 7 of them rapidly within 10 - 21 days after SMZ/TMP administration and the other 2 patients within 27 and 33 days respectively. One infant improved but died afterwards of complications not related to the treatment.

No hematological nor cutaneous and gastrointestinal side effects were observed. The liver and renal function test performed on 3 out of 10 cases on the first few days of the commencement of treatment and 3 weeks later, were all within normal limits.

Our experience with the use of parenteral SMZ/TMP in infants with bacterial meningitis not responding to conventional microbial therapy gave encouraging results.

Presented at the 11th Seminar on Tropical Medicine, Yensei University, Seoul 9 - 11 June, 1980.

Introduction

In dealing with cases of purulent meningitis the following points should be taken into consideration :

1. The most frequent gram negative bacteria as the causative agent as reported by some authors are E. coli and Salmonella (Riley, 1972; Sabel and Brandberg, 1975).
2. The susceptibility of an organism, especially the Gram — negative bacilli to various antimicrobial agents might change with time and particularly with the recent increasing use of antibiotics.
3. Host resistance in various cases is variable, such as cases of neonates who are less resistant to Gram-negative bacteria due to lack of IgA and IgM. (Gotoff and Behrman, 1970).
4. In vitro experiments on susceptibility not only take a long time before results are obtained but also the special virtue in vivo is less reliable (Mc. Cracken, 1972).
5. In the case of purulent meningitis, antimicrobial agents have shown different effects on the penetration through the "blood brain barrier" (Sabel and Brandberg, 1975).

Based on the above facts, in an effort to minimize the mortality and morbidity of purulent meningitis, the initial therapeutic management before the bacteriological examinations are obtained will be reemphasized in this paper.

Concerning the increasing occurrence of purulent meningitis as well as the persisting high mortality rate and side effects during the last decade, physicians are very much concerned about the failure of medical treatments on these cases, both clinically and bacteriologically (the persisting microbial agent in cerebrospinal fluid) although various kinds of drugs have been used which are thought to have a broad spectrum antimicrobial agent (a combination of ampicillin and gentamicin) (Monizaria et al., 1969; Sabel and Brandberg, 1975).

Nevertheless, today there is a combined preparation of SMZ/TMP which has a synergistic effect, both in vitro and in vivo, and is considered to have a broad spectral
has been proven in various infections, including cases of purulent meningitis. This combination is reported to have a good penetration toward the "blood brain barrier". One hour after therapeutical administration, SMZ concentration in blood is about 60-240 ug/ml, that in liquor is around 25 - 50 ug/ml; whereas TMP concentration in blood and liquor is approxifately 0,3-1,5 ug/ml (its concentration in liquor might reach $^1/_3$ — $^1/_4$ of that in blood) (Angehrn and Then, 1973; Sabel and Brandberg, 1975).

Some authors also reported that the sensitivity of this combination against Gram-negative bacteria (e.g. E. coli) was still around 80 - 90%, whereas that of other drugs such as ampicillin was only 20% and 50%. Thus it was considered to be relatively sensitive.

Material and methods

This investigation was based on a retrospective study on 10 cases of purulent meningitis at the Department of Child Health, Medical School, University of Indonesia, from February 10, 1978 to March 22, 1980. Five patients ranging in age from 2 to 43 days and 5 other patients from 2 to 9 months were included in this study.

These patients were suffering from purulent meningitis and were considered therapeutic failures after conventional microbial therapy (chloramphenicol, ampicillin, cloxacillin, gentamicin and amikin).

At the same time 116 patients with purulent meningitis were treated at the same hospital.

The diagnosis of purulent meningitis was based on clinical findings and laboratory examination of the cerebrospinal fluid.

Conventional treatment administered was a combination of drugs with the following dosages; intravenous daily dose of 100 mg/kg BW chloramphenicol, intravenous daily dose of 300 - 400 mg/kg BW ampicillin given every 4 hours, 100 mg/kg BW cloxacillin and gentamicin with the daily dose of 7,5 mg/kg BW divided in 2 doses given every 12 hours for the first 3 days followed by 5 mg/kg BW and amikin as a substitute for gentamicin, given 15 mg/kg BW intramuscularly divided in two doses every 12 hours.

Antibiotic therapy was altered indicated by clinical and laboratory criteria. Clinical criteria referred to still persisting symptoms of fever, convulsion, hyperirritability and body weight gain of the patients; whereas cerebrospinal fluid examination for number of cells and glucose content and peripheral blood leucocytes comprised laboratory criteria.

A combination of sulphamethoxazole and trimethoprim was given intravenously with the daily dose of 10 mg TMP/kg BW/day for the first 3 days followed by 6 mg/kg BW/day which was divided in 2 doses every 12 hours and administered slowly for about 1 hour.

Daily close clinical observations were done to evaluate the progress of therapy, complications and side effects of the treatment.

Liver and renal function tests were performed on 3 patients only, because of technical difficulties, on the first day of treatment and 21 days later.

Cerebrospinal fluid examination was carried out on admission.
tion was repeated on treatment day 10 for evaluation of the outcome. When the improvement was not satisfactory yet, the whole treatment was continued until the patient recovered. The treatment in neonates was continued for 3 weeks.

Further evaluation after discharge from hospital was done at the outpatient clinic of the Division of Pediatric Neurology.

Results

The most frequent sign of purulent meningitis in our series was fever, whereas convulsion was found in 8 out of 10 cases (Table 1). The diagnosis of purulent meningitis was established in 2 cases after lumbar puncture was performed and these patients were diagnosed as sepsis on admission. Decreased level of conciousness was found in 2 cases.

We found Acute otitis media (1 case), bronchopneumonia (2 cases), paralytic ileus (1 case) and septicemia (3 cases) as the accompanying

Table 2 shows that 5 cases were less than 43 days old, whereas the other 5 cases were between 2 - 9 months. Cerebro spinal culture was negative in 7 cases. Pseudomonas was found in 2 cases (case no. 6 & 10) which was already resistant to gentamicin and sulvencillin (resistancy test to SMZ was not done), whereas Streptococcus pneumoniae was found in one case (case no. 2) which was still sensitive to ampicillin and gentamicin. During the course of illness some complications and or accompanying diseases
ventriculitis (3 cases), subdural effusion (1 case). The types and times of administration of various antibiotics in combination can be seen in table 2. Those antibiotics have been given for 14 to 48 days, except case no. 10 who had been given 3 antibiotics i. e. ampicillin, cloxacillin and gentamicin or amikin as its substitute. After having conventional treatment there was no improvement either clinically or laboratorically.

Table 3 shows that the hyperirritability and fever were clearly seen in all cases, whereas in 2 out of the 10 cases convulsion was still observed. The result of cerebrospinal fluid examination in 10 cases showed a worsening in 3 patient whereas in 6 patients a decrease of cell count was noticed but still above normal and low glucose was still present (40 mg% or less in 6 patients and less than 50 mg% in the other 4 patients), whereas the protein value was still high (between 85,5 to 427 mg%).

After being treated with SMZ/TMP in combination, 7 out of the 10 cases showed rapid improvement (between 10-21 days), in 2 cases the improvement was between 27 and 33 days whereas in 1 case clinical improvement was seen in day 15, but this case finally died on day 32 because of the accompanying diseases which were not related to the SMZ/TMP treatment i.e. ventriculitis Morbus Hirschprung (see table 4).

The criteria of clinical improvements were the disappearance of fever and hyperirritability, the child became alert, the emerging of sucking reflex and the improvement of other neurologic conditions. On discharge from the hospital all of the patients were in active condition and free from fever. They were requested to return to the outpatient clinic of the pediatric neurology division for a regular follow up. On regular follow up

neurologic sequelae were found in 4 out of 6 patients. They were hydrocephalus (2), vision disorder (1) and in one patient spasticity of the extremities was observed.

The liver and renal function tests in 3 cases (case no. 6, 9 and 10), were within normal limits. During treatment with SMZ/TMP, no side effects on the skin, blood and G.I. tract were found.

Discussion

The combination of ampicillin and gentamicin has been used in purulent meningitis for the last 10 years. Several authors reported the tendency of the rising resistancy especially the gram negative bacilli to ampicilin (Linberg et al., 1977). The aminoglycoside especially gentamicin was potent enough to combat gram negative bacilli, but the treatment required a long course, sometimes the susceptibility to antimicrobial changed during the course of treatment, giving unsatisfactory results. Although the penetration of gentamicin to the sick meningen as in purulent meningitis, is better compared to the normal meningen, the penetration of this antibiotic into the cerebrospinal fluid is extremely poor, so that the concentration does not reach the MIC (compared to ampicillin which can reach a concentration in the cerebrospinal fluid up to 10 - 100 times of the MIC). Direct administration into the ventricle/intrathecal space had been tried, using only a low dose because of the unwanted irritative reaction (Mc. Cracken, 1972; Chemotherapeutic Routes in Meningitis, 1976).

On the other hand good results of the SMZ/TMP combination in the treatment of purulent meningitis have been reported (Morizaria et al., 1969; Calonghi and Lelasi, 1972; Sabel and Brandberg, 1975). The superiority of this drug was due to its high penetration effect.

In a research, the concentration in the cerebrospinal fluid could reach $\frac{1}{4}$ to $\frac{1}{3}$ of its level in the blood. It has also been reported that the change of resistancy during or after the treatment was very low. Both drugs in a combination are synergistic and give a broad spectrum antimicrobial effect (Avery, 1971; Bergan and Brodwall, 1972 and Kirwan, 1974). The side effect of SMZ/TMP has not been reported yet, except that this drug was not advisable to be used in very young cases (less than 7 days), in infants with a low birth weight and icterus. But, taking into consideration that this drug is metabolised in the liver and is excreted by the kidney, it is advisable to strictly control the possible organic disorders during treatment (Calonghi and Lelasi. 1972; Sabel and Brandberg, 1975).

Acknowledgement

The authors express their gratitude to The Roche Far East Research Foundation for the supply of the drugs and expenses needed in this study.

TABLE 1 : *Data of the patients before admission.*

Case No.	Sex	Age		Body weight (gram) at onset	Presenting symptoms or signs	Decreased level of consciousness	Predisposing factors
		Months	days				
1.	M	5	—	7000	Fever, Convulsion	+	Otitis Media Bronchopneumonia
2.	M	9	—	7000	Fever, Convulsion	+	Bronchopneumonia Paralytic Ileus
3.	M	2	—	4500	Fever, Convulsion	—	—
4.	F	2	—	5000	Fever, Convulsion	—	—
5.	M	5	—	6650	Fever, Convulsion	—	—
6.	M	—	20	4000	Fever, Diarrhea	—	Septicemia
7.	F	—	23	2950	Fever, Convulsion	—	Morbus Hirschprung
8.	F	1	13	4300	Convulsion	—	—
9.	M	—	2	2950	Fever, Convulsion Vomiting	—	Septicemia
10.	M	—	21	4900	Fever	—	Septicemia

TABLE 2: *Data of the patients and therapy given before SMZ/TMP treatment.*

Case No.	Sex	Age		Bacteria isolated		Complications	Conventional Microbial Therapy	
		Months	Days	C S F	Blood		Drugs	Days
1.	M	5	—	0	0	—	Amp. Chlo.	20 20
2.	M	9	—	Strep pneumoniae	0	—	Amp. Chlo.	19 19
3.	M	2	—	0	0	—	Amp. Gent.	14 14
4.	F	2	—	0	0	—	Amp. Gent.	21 21
5.	M	5	—	0	0	Paresis of the extremities	Amp. Cloxa.	48 6
6.	M	—	20	Pseudomonas sp.	0	Ventriculitis	Amp. Cloxa.	48 24
7.	F	—	23	0	0	Ventriculitis	Amp. Gent.	19 19
8.	F	1	13	0	0	Subdural effusion	Amp. Gent.	21 21
9.	M	—	2	0	0	—	Amp.	24
10.	M	—	21	Pseudomonas sp.	0	Ventriculitis	Amp. Cloxa. Gent. Am.	38 14 10 28

Am. = Amikin Chlo. = Chloramphenicol Gent. = Gentamicin
Amp. = Ampicillin Cloxa. = Cloxacillin

TABLE 3 : *Data suggesting therapeutic failures*

Case No.	Body weight (gram)		Fever		Hyperirri-tability		Convul-sion		C S F						WBC/mm³	
									White cells (mm³)		Glucose (mg/100 ml)		Protein (mg/ 100 ml)			
	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
1.	7000	7050	+	+	+	+	+	—	TNTC	272	45	49	162,9	140	24400	19600
2.	7000	7050	+	+	+	+	+	—	TNTC	437	44	40	90,2	85,5	25200	5200
3.	4500	4600	+	+	+	+	+	—	120	72	45	44	342	209	9400	10000
4.	5000	5400	+	+	+	+	+	—	TNTC	146	47	40	428	328	7000	8400
5.	6650	6900	+	+	+	+	+	—	TNTC	435	38	45	125,6	160,3	9000	16600
6.	4000	4150	+	+	+	+	+	+	2218	TNTC	49	35	114	129	11200	16800
7.	2950	3000	+	+	+	+	+	—	TNTC	TNTC	41	38	276,5	126,4	7800	4200
8.	4300	4100	+	+	+	+	—	—	3400	416	50	45	488,6	214	6400	6400
9.	2950	2900	+	+	+	+	—	—	51	77	36	40	256,4	424,7	5000	7800
10.	4900	4500	+	+	+	+	+	+	1109	TNTC	38	34	157,8	427,5	15000	11600

I = At onset
II = After conventional microbial therapy
TNTC = Too numerous to count

TABLE 4: *SMZ/TMP treatment, length of treatment and results*

Case No.	Length of treatment (days)	Results	Follow up
1.	10	Recovered	No sequelae
2.	16	Recovered	No follow up
3.	12	Recovered	Vision disorders
4.	19	Recovered	Hydrocephalus
5.	33	Recovered	Spasticity
6.	21	Recovered	No sequelae
7.	32	Died on day 32	—
8.	13	Recovered	No follow up
9.	27	Recovered	No follow up
10.	21	Recovered	Hydrocephalus

REFERENCES

1. ANGEHRN, P. and THEN, R. : Investigations on the Mode of Action of the Combination Sulphamethoxazole — Trimethoprim. Chemotherapy (Basel) 19 : 1 (1973).
2. AVERY, G.S. (ed): Evaluations on new drugs; Trimethoprim — Sulphamethoxazole. Drugs. 1 : 7 (1971).
3. BERGAN, T. and BRODWALL, E.K. : Human Pharmacokinetics of a Sulphamethoxazole — Trimethoprim combination. Acta Med. Scand. 192 : 483 (1972).
4. CALONGHI, G.F. and LELASI, G. : Intravenous therapy with a combination of Sulphamethoxazole-Trimethoprim in Purulent Meningitis (translation). G. Mal Infett. Parassit. 24 : 9 (1972).
5. CHEMOTHERAPEUTIC ROUTES IN MENINGITIS (Editorial). Br. med. J. — : 977 (1976).
6. GOTOFF, S.P. and BEHRMAN, R.E. : Neonatal septicemia, J. Pediatr. 76 : 142 (1970).
7. KIRWAN, W.O. : Cerebrospinal Fluid Co-trimoxazole Levels. J. Irish med. Ass. 67 : 76 (1974).
8. LINDBERG, J.: ROSENHALL, U.: NYLEN, O. and RINGER, A. : Longterm outcome of Hemophilus influenzae meningitis related to Antibiotic treatment. Pediatrics 60 : 1 (1977).
9. MC CRACKEN, G.H. Jr.: The rate of bacteriologic response to antimicrobial therapy in Neonatal Meningitis. Am. J. Dis. Child. 123 : 547 (1972).
10. MORIZARIA, R.N.; WALTON, I.G. and PICKERING, D. : Neonates Meningitis treated with Trimethoprim and Sulphamethoxazole. Br. med J. II : 512 (1969).
11. RILEY, H.D. Jr. : Neonatal Meningitis (Editorial). J. infect. Dis. 125 : 420 (1972).
12. SABEL, K.G. and BRANDBERG, A. : Treatment of Meningitis and Septicemia in Infancy with Sulphamethoxazole-Trimethoprim combination. Acta Pediatr. scand. 64 : 25 (1975).