A CLINICAL TRIAL OF AMPICILLIN *VERSUS* TRIMETHOPRIM-SULFAMETHOXAZOLE IN THE TREATMENT OF SHIGELLA DYSENTERY

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PREFACE

The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) is an autonomous, international, philanthropic and non-profit centre for research, education and training as well as clinical service. The Centre is derived from the Cholera Research Laboratory (CRL). The activities of the institution are to undertake and promote study, research and dissemination of knowledge in diarrhoeal diseases and directly related subjects of nutrition and fertility with a view to develop improved methods of health care and for the prevention and control of diarrhoeal diseases and improvement of public health programmes with special relevance to developing countries. ICDDR,B issues two types of papers: scientific reports and working papers which demonstrate the type of research activity currently in progress at ICDDR,B. The views expressed in these papers are those of authors and do not necessarily represent views of International Centre for Diarrhoeal Disease Research, Bangladesh. They should not be quoted without the permission of the authors.

ABSTRACT

Following a nationwide outbreak of *Shigella dysenteriae* type 1 and the recognition of shigella isolates resistant to ampicillin, the drug of choice, we conducted a clinical trial to compare the efficacy of ampicillin vs trimethoprim-sulfamethoxazole for the treatment of shigella dysentery. Patients with symptoms of dysentery and no other complicating illness were randomized into one of two treatment groups. Patients in the two groups were comparable at the time of hospital admission with regard to age, sex, presenting complaints and shigella strains. They responded well with both regimens and there was no significant difference in the mean time until stool became culture negative (1.4 days), temperatures returned to normal (2.7 days) and fecal WBCs disappeared (3.0 days); abdominal pain, tenesmus and stool blood and mucus improved significantly more rapidly with trimethoprim-sulfamethoxazole than with ampicillin. There was no evidence of toxicity with either drug. While both drugs are effective for the treatment of shigella dysentery, trimethoprim-sulfamethoxazole was considered to be superior.

INTRODUCTION

Shigellosis is a major health problem in Bangladesh and other developing countries (Tito de Marias *et al.*, 1966, Khan and Curlin 1974, Gangarosa *et al.*, 1973). A recent nationwide outbreak of *Sh.dysenteriae* type 1, or Shiga bacillus, resulted in many deaths and complications (Khan *et al.*, 1975, Rahaman *et al.*, 1975). During and after this outbreak, resistance of Shigella, particularly *S.dysenteriae* type 1, to common antibiotics was first noted in Bangladesh (Rahaman *et al.*, 1974). Mutanda (1981) found that 6% of 87 Shigella strains isolated in 1979 were resistant to ampicillin and that 6 were resistant to several antibiotics. Such resistance has occurred elsewhere to most safe and useful agents. In the United States, for example, 17% of *Sh.flexneri* and 45% of *Sh.sonnei* in 1974 were resistant to ampicillin, the previous drug of choice (Nelson *et al.*, 1976). The appearance of ampicillin resistance in Bangladesh and the high prevalence of skin rash with this drug raised the need for alternative antibiotics. Accordingly, a study was conducted to compare trimethoprim-sulfamethoxazole and ampicillin for the treatment of shigella dysentery in rural Bangladesh.

SUBJECT AND MATERIALS

The study was performed at the rural treatment centre of the International Centre for Diarrhoeal Disease Research, Bangladesh (formerly the Cholera Research Laboratory) located in Matlab thana, Comilla district, about 45 km south-east of Dacca. This centre in operation since 1963 provides diarrhoeal treatment services to 4000-6000 patients per year from a well defined study area. Details of the study area, its people and field research procedures have been reported previously (International Centre for Diarrhoeal Disease Research, Bangladesh (1978), Scientific Report No. 9). About 6% of these patients have shigellosis. This study was conducted during the period from 1977 to 1979.

Patients with symptoms of dysentery, abdominal pain, tenesmus, and fever who were suspected clinically to have shigella were considered for the study. We excluded pregnant women, children below three months of age, and patients with a history of adverse reaction to penicillin or sulfanomide, a complicating illness (e.g., pneumonia, UTI) or a history of prior treatment. Patients meeting these criteria were asked to enroll in the study and after obtaining the informed consent of the patient or their guardian, they were assigned to a treatment group according to a random number table.

A full clinical examination of the patients was done after admission. Before therapy was begun, a stool specimen was collected and sent for microscopic examination, a rectal swab for culture, and urine for analysis, and blood for white blood cell, differential and platelet counts. Treatment was started with either trimethoprim-sulfamethoxazole or ampicillin trihydrate as a tablet or suspension. Trimethoprim-sulfamethoxazole was administered at a dose of 6 mg/kg/day 12 hourly for 5 days. Ampicillin was given in a dose of 50 mg/kg/day in six hourly divided doses to patients weighing 15 kg or more and in double dose for smaller children. Daily stool was cultured on taurocholate tellurite gellatin agar, shigella-salmonella agar, and MacConkey agar plates during hospitalization until these were negative for three consecutive days.

If *Salmonella sp.* or *V.cholerae 01* were isolated, the patient was dropped from the study. Daily stool microscopy was performed on three consecutive days to exclude vegetative amoeba and giardia and to determine when the stool became free of leukocytes (<10 leukocytes/hpf). Shigella isolates were typed with specific antisera and were tested for antibiotic resistance to trimethoprim-sulfamethoxazole, ampicillin, tetracycline, streptomycin, chloramphenicol, gentamycin, and kanamycin using the Bauer-Kirby (1966) technique. Oral rehydration solution or intravenous acetate solution was given as required, intake and output was measured every 8 hours, and vital signs were recorded every 4 hours. No other medications were given.

A daily record was kept for each patient noting the stool characteristics, (volume, consistency, presence of blood and mucus), fever, presence of abdominal pain, tenesmus, and hydration status. Drug toxicity was monitored with a haematocrit, white blood cell and differential counts, platelet count and urine analysis performed before, during, and after treatment. The presenting characteristics of the patients were compared using a chi-square statistic. The duration of outcome parameters were examined using the Kolmogorov-Smirnov Goodness of Fit Test.

RESULTS

One hundred and eighteen patients ranging from 6 months to 65 years of age were entered into the study and randomized to either the ampicillin (55) or the trimethoprim-sulfamethoxazole (63) treatment groups. Patients in the two groups were comparable with respect to age, sex, presenting complaints, stool exam, and the

shigella strains isolated (Table I). On admission, the percent of patients presenting with fever of 101°F or more (30% vs 28%), severe dehydration (14% vs 15%), or the mean initial WBC (16,000 vs 15000) did not differ significantly between groups.

The outcome of treatment for patients receiving either regimen was good. However, patients who took trimethoprim-sulfamethoxazole had a significantly shorter duration of fever (mean 1.3 vs 1.5 days) abdominal pain (mean 2.8 vs 3.6 days) and persisting stool mucus (mean 3.9 vs 4.9) and blood (mean 1.5 vs 2.2 days) than those taking ampicillin (Figure 1). There was no difference in the number of days after beginning treatment that the stool of most patients became culture negative for Shigella (3 days) or cleared of fecal leukolytes (<10/hpf) (6 days). Two patients in the ampicilling group had ampicillin sensitive shigella in their stool 4 days after treatment began. Another 2-year old female child, in the ampicillin group had clinical dysentery for 14 days even though her stool had no shigella after day 2. On day 14, she was treated with trimethoprim-sulfamethoxazole and recovered within 48 hours. The mean WBC count and the percent of bands had returned to normal in both groups 5 days after treatment began.

Most of the 118 shigella isolates tested were sensitive to ampicillin (93%), trimethoprim-sulfamethoxazole (97%), as well as kanamycin (98%), gentamycine (100%), and chloramphenicol (96%) and resistant to streptomycin (91%) and tetracycline (93%) (Table II). Three patients who received ampicillin had ampicillin-resistant shigellae and while all cleared their organisms by the third day, they had longer duration of symptoms. One patient with a trimethoprim-sulfamethoxazole resistant isolate was treated with this drug and had a good clinical response with clearance of shigella in three days. No clinical or laboratory evidence of drug toxicity was noted but two patients who received ampicillin and three who received trimethoprim-sulfamethoxazole developed oral thrush.

DISCUSSION

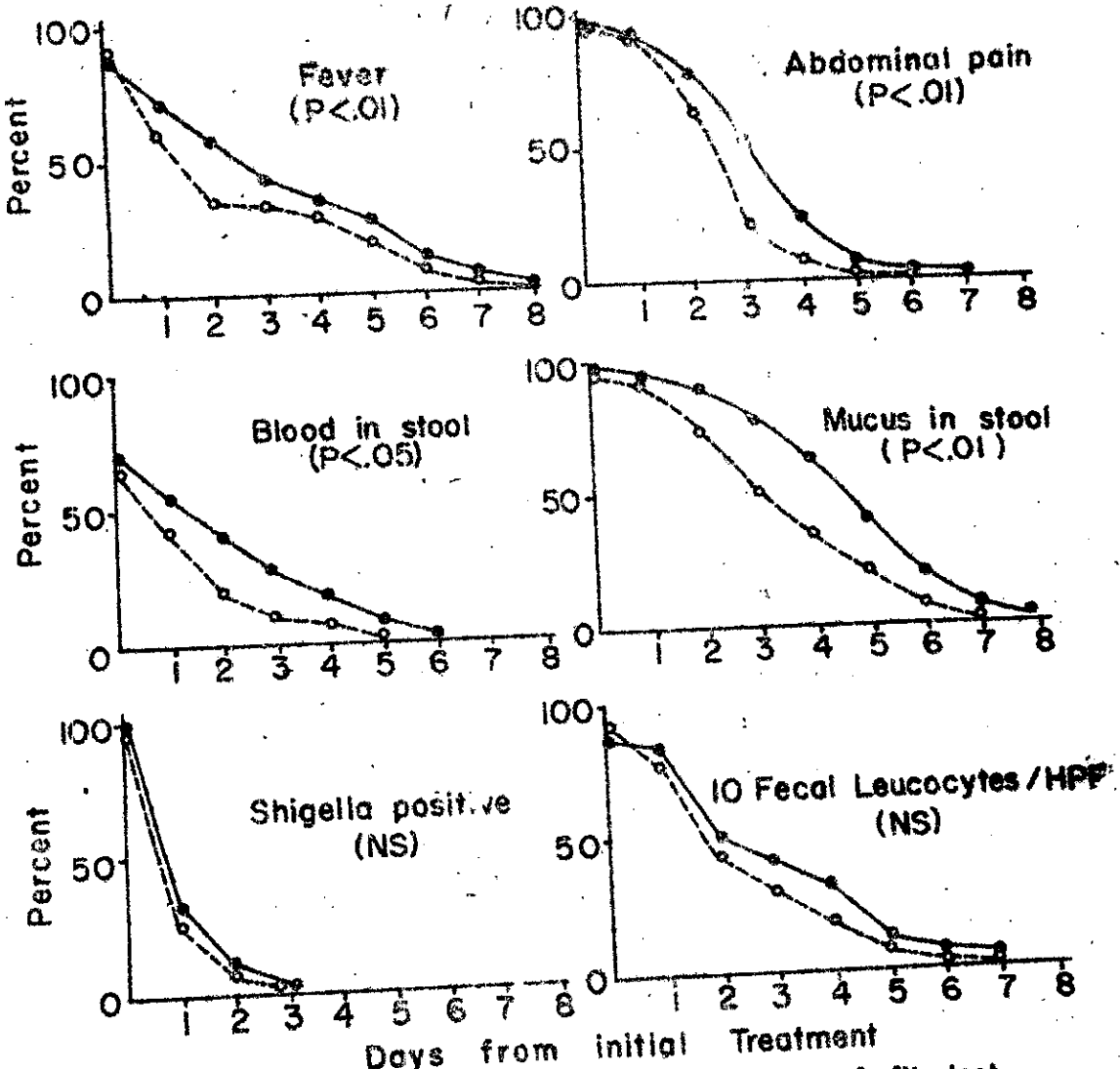
Trimethoprim-sulfamethoxazole is active against the wide range of both gram positive and gram negative organisms and has proved effective in the treatment of urinary tract infections, chronic bronchitis, pneumonia, gonorrhoea, enteric fever, and other infections. In vitro, shigella are highly sensitive to trimethoprim-sulfamethoxazole (Ruddy *et al.*, 1974) even in areas where ampicillin resistant strains have become predominant (Jarvis *et al.*, 1970).

TABLE I--COMPARISON OF SHIGELLA PATIENTS RANDOMIZED TO AMPICILLIN (AMP) VS TRIMETHOPRIM-SULFAMETHOXAZOLE (TMS) TREATMENT GROUP

Comparison	Percent of Total AMP (N=55)	TMS (N=63)	P Value*
Age (years)			
0-4	58	59	NS
5-14	14	16	
15+	28	25	
Sex - % Male	64	65	NS
Presenting Complaints			
Abdominal pain	98	100	NS
Tenesmus	98	97	NS
Blood in stool	89	92	NS
Vomiting	57	49	NS
Fever	95	97	NS
Stool examination			
WBC ≤10	11	9	NS
11-25	23	29	
26+	66	62	
Blood	63	63	NS
Mucous	96	97	NS
Shigella strains			
dysenteriae type 1	47	47	NS
flexneri	45	44	
Other	8	9	

* CHI square test

COMPARISON OF OUTCOME OF TREATMENT OF PATIENTS RECEIVING AMPICILLIN (•) VS TRIMETHOPRIM SULFAMETHOXAZOLE (°) FOR SHIGELLA DYSENTERY



Pvalue by kolmogorov-Smirnov goodness of fit test

TABLE II--ANTIBIOTIC RESISTANCE PATTERN OF SHIGELLA STRAINS ISOLATED DURING THE TREATMENT TRIAL AT MATLAB, 1977 - 1979

Antibiotics*	% Resistant			
	Shiga (N=55)	Flexneri (N=53)	Others (N=10)	Total (N=118)
Tetracycline	93	74	75	93
Ampicillin	5	7	20	7
Chloramphenicol	0	8	0	4
Kanamycin	0	5	0	2
Gentamicin	0	0	0	0
Streptomycin	94	89	80	91
Trimethoprim-sulfamethoxazole	5	0	20	3

* Disc Sensitivity.

Trimethoprim-sulfamethoxazole has proved effective previously in clinical studies for the treatment of shigellosis (Mabadeje 1974, Udom Lexombonn *et al.*, 1972). Nelson (1976) concluded from a trial similar to our own that trimethoprim-sulfamethoxazole is the best currently available drug in areas where multiple antibiotic resistance is common. The present study has confirmed these findings in a different geographical location where the shigella strains are predominantly flexneri and *dysenteriae* type 1 and where ampicillin resistance has begun to occur.

Several features of the current study should be emphasized. All patients were treated in a field hospital and had clinically severe dysenteric forms of shigellosis based on our strict entrance criteria requiring dysentery, fever, abdominal pain and tenesmus. Furthermore, nearly 50% of our isolates were *S.dysenteriae* type 1 known to produce more severe dysentery with complications such as leukomoid reaction and haemolytic uremic syndrome (Koster *et al.*, 1978). Both ampicillin and trimethoprim-sulfamethoxazole were effective in this simple field setting but patients treated with trimethoprin-sulfamethoxazole had a shorter duration of fever, abdominal pain tenesmus and stool blood mucus. Almost all patients cleared their stool of shigella within 3 days including 3 patients in the ampicillin group who had ampicillin resistant isolates. The prolonged duration of symptoms in these 3 patients suggests that in vitro sensitivity testing does correlate with clinical response to treatment even though other mechanisms were probably important in bacterial clearance.

Recovery from shigella proceeded with daily improvements in different indicators of disease. Clearance of shigella from the stool in the majority of cases occurred within one day of initiating treatment and was followed successively by clearance of stool blood (median time one day), fecal leukocytes (median time 2 day) and the return of normal body temperature (median time 2 days). Relief of abdominal pain and clearance of mucus from the stool occurred with a median time of three and four days respectively. These observations are consistent with our clinical impression that recovery from shigella dysentery can be prolonged due to the process of healing tissue invasion.

In summary, trimethoprim-sulfamethoxazole and ampicillin are both effective in the treatment of severe shigellosis. While candida is a recognized side effect of ampicillin treatment, we found an almost equal number of patients with oral thrush in each treatment group. Few of the shigella isolated in this study were resistant either to ampicillin (3) or trimethoprim-sulfamethoxazole (1). Patients treated with trimethoprim-sulfamethoxazole recovered from their symptoms more rapidly and may make it a preferred antibiotic in treating severe shigella dysentery. The pattern of antibiotic resistance does seem to correlate with clinical recovery and should be monitored to insure the most effective therapy.

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