Erythromycin and Trimethoprim-sulphamethoxazole in the Treatment of Cholera in Children

Iqbal Kabir, Wasif Ali Khan, Rukhsana Haider, Amal K Mitra, and Ahmed Nurul Alam

International Centre for Diarrhoeal Disease Research, Bangladesh, GPO Box 128, Dhaka 1000, Bangladesh

International Centre for Diarrhoeal Disease Research, Bangladesh, GPO Box 128, Dhaka 1000, Bangladesh

ABSTRACT

To evaluate the efficacy of erythromycin and trimethoprim-sulphamethoxazole (TMP-SMX) in the treatment of cholera in children aged 1-8 years, a randomised clinical trial was conducted at a diarrhoea treatment centre in Bangladesh from December 1991 to June 1992. Fifteen children received erythromycin, 50 mg/kg per day, in four equally divided doses, 18 children received 10 mg/kg per day of trimethoprim and 50 mg/kg per day of sulphamethoxazole in two equally divided doses (12 hourly) for five days, and 15 children received no antibiotic; children in all three groups received intravenous cholera saline for severe dehydration and for mild to moderate dehydration, a rice-based oral rehydration solution. The mean stool volumes in mL/kg body weight in the two treatment groups were less than that of the control group, and there were no significant differences in stool volume among the two treatment groups. However, 67% of the children in the erythromycin group and 82% in the TMP-SMX group recovered within 72 hours compared to 33% in the control group ($p<0.01$). Similarly, the bacteriological cures were 80% in the erythromycin group and 83% in the TMP-SMX group compared to only 27% in the control group ($p<0.001$). These results confirm that both erythromycin and trimethoprim-sulphamethoxazole are effective antimicrobials in the treatment of cholera. These drugs are of value specially in younger children in whom tetracycline is contraindicated or when the infecting *Vibrio cholerae* are resistant to tetracycline.

***Key words*: Cholera;** *Vibrio cholerae;* Erythromycin; Trimethoprim; Sulphamethoxazole; Drug-resistance, Microbial

INTRODUCTION

Cholera, the most severe of all infectious diarrhoeal diseases, is an important cause of morbidity and mortality in many developing countries. The disease is endemic in some parts of Asia, Africa, and South America (1). It is characterised by acute onset of vomiting, profuse watery diarrhoea, and development of dehydration that might lead to death if not timely treated (2,3). The advent of oral rehydration solution (ORS), however, has simplified the management of cholera and substantially reduced the mortality due to dehydration. Appropriate antibiotics, including tetracycline, doxycycline, furazolidone, and chloramphenicol, given concurrently with fluid and electrolyte replacement, reduce the volume of stools, the duration of diarrhoea, and the excretion of *Vibrio cholerae* in faeces (4-7).

However, tetracycline can not be prescribed to pregnant women and younger children due to its adverse effects on teeth and growing bone. Moreover, there have been frequent reports of multiple drug-resistant *V. cholerae,* including tetracycline and furazolidone (8-11). It is, therefore, important to identify effective alternative antimicrobials for the treatment of cholera in children and pregnant mothers and also for large-scale epidemic due to tetracycline and furazolidone-resistant strains of *V. cholerae*. Previous studies have shown good clinical and bacteriological cures of erythromycin and trimethoprim-sulphamethoxazole in cholera, but those studies were done nearly 20 years back, and by this time, antimicrobial susceptibility

to *V. cholerae* O1 might have changed. The present pilot study was undertaken to evaluate the clinical efficacy of erythromycin and trimethoprim-sulphamethoxazole in the treatment of cholera in children.

Correspondence and reprint requests should be addressed to:
Dr. Iqbal Kabir *E-mail:* **ikabir@icddrb.org**

PATIENTS AND METHODS

Patients

The study was carried out at the Clinical Research Centre of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). Patients enrolled in this study were only boys, aged 1-8 years, having a history of watery diarrhoea for less than 48 hours, and their stool containing motile *V. cholerae* as seen under a dark-field microscope. Patients who had taken antibiotics before hospital admission, and patients with systemic infections were excluded from the study.

Clinical management

On admission, body weight was obtained, and the patients were nursed on a cholera cot. A thorough clinical examination was performed, and the hydration status was assessed clinically by a physician according to World Health Organization (WHO) criteria. A stool specimen was sent to the laboratory for the dark-field microscopy to detect motile *V. cholerae* and another specimen for bacteriological culture. For patients with mild to moderate dehydration, a rice-based oral rehydration solution (R-ORS) was started (12). Children with severe dehydration were rehydrated with an intravenous solution, containing 133 mmol of sodium, 13 mmol of potassium, 98 mmol of chloride, and 48 mmol of acetate in one litre of water. Complete rehydration was achieved within 4-6 hours of admission. All stools, urine, and vomit were collected separately. The volumes of intravenous fluid, amount of R-ORS intake, volumes of stools and urine were recorded every 8-hour period, beginning at the time of admission and continued until the diarrhoea stopped. The patients stayed in the hospital for 5 days, or until the diarrhoea resolved.

Randomisation

After rehydration, the patients were randomly assigned to one of the two treatment groups (erythromycin or trimethoprim-sulphamethoxazole), or to the no-antibiotic control group by using sealed envelopes containing a numeric treatment code obtained from a table of random numbers. Erythromycin was given at 50 mg/kg per day in 4 equally divided doses, trimethoprim at 10 mg/kg per day and sulphamethoxazole 50 mg/kg per day in two equally divided doses for five days. The justification for including a non-antibiotic group as control is that replacement of fluid and electrolytes is the cornerstone therapy for the prevention of death due to dehydration. However, antibiotic therapy has been shown to reduce the duration of diarrhoea and accelerate bacteriological cure.

Bacteriology

Rectal swab specimens were obtained from the patients before starting the treatment and subsequently daily for five days. Faecal specimens were immediately plated onto MacConkey's Salmonella-Shigella and Monsur's (taurocholate-tellurite gelatine agar) media plates. Bacteria from colonies typical of *V. cholerae* were tested for agglutination with a polyvalent O group 1 antiserum.

Measurements of outcome variables

The outcome variables include volume of stool in mL which was measured every 8 hours, ORS and intravenous fluid intake, the duration of diarrhoea in hours, and the duration of *V. cholerae* excretion in stools. Duration of diarrhoea was defined as the end of the last 8-hour period in which a liquid stool was passed. Clinical success was defined as the end of diarrhoea occurring on or before 72 hours without subsequent relapse, and clinical failure was defined if diarrhoea continued beyond 72 hours. A period of 72 hours was selected because in most patients treated with appropriate antibiotics, diarrhoea usually resolves within this period (6). Similarly, bacteriological success was defined if the stool culture became negative on day 3 or before, and remained negative afterwards.

Statistical analysis

The significance of differences in means was tested by the Student's *t* test. Analysis of ariance (ANOVA) or Krushkal-Wallis test was done when appropriate, and the proportion of success was tested by the chi-squire or Fisher's exact test. A value of $p<0.05$ was considered significant.

RESULTS

Initially, 54 patients were positive for *V. cholerae* by dark-field microscopic examination of their stools. Six patients were excluded, because stool culture failed to grow *V. cholerae*. Of the remaining 48 children, 15 received erythromycin, 18 trimethoprim-sulphamethoxazole, and 15 no antibiotics. The admission characteristics, including the age, duration of diarrhoea, hydration status, and stool pathogens, are shown in Table I. There were no significant differences in these variables among three treatment groups of children on admission.

Table II shows the clinical outcome of three groups after treatment with erythromycin, trimethoprim-sulphamethoxazole or without any antibiotic. The means of total faecal output, expressed as mL/kg, were not significantly different from the two treatment groups when compared with the control group. However, the mean duration of diarrhoea was significantly less in both the erythromycin and TMP-SMX groups compared to the control group ($p<0.03$). The number of children who had clinical cure was 67% and 83% for the erythromycin and the TMP-SMX groups respectively. Both proportions are significantly different from the only 33% in the control group. Similarly, the bacteriological cure was 80% for the erythromycin and 83% in the TMP-SMX groups compared to only 27% in the control group ($p<0.001$) (Table II).

Table I. Admission characteristics of children with cholera in the three treatment groups

	Treatment groups		
Characteristic	Erythromycin	TMP-SMX*	Control
Number of patients	15	18	15
Age (months)	57±34	57±29	61±35
Body weight, kg	11.3±4.0	12.7±3.7	13.3±3.9
Preadmission hours of diarrhoea	12±6	11±7	13±4
Dehydration status (No. of children)			
Mild to moderate	4	8	6
Severe	11	10	9
Serotypes of *V. cholerae* O1 El Tor			
Ogawa	14	16	13
Inaba	1	2	2

Values are mean ±SD.
*Trimethoprim-sulphamethoxazole

Antibiotic sensitivity of *V. cholerae* was determined in 30 isolates. It showed 100% sensitivity to tetracycline (30/30; confidence limits [CL] 88% to 100%), 87% to both erythromycin and trimethoprim-sulphamethoxazole (26/30; CL 69% to 96%), and only 13% to furazolidone (4/30; CL 4% to 31%). The overlapping confidence limits indicate the absence of statistically significant differences between the antimicrobial agents used in our two study groups.

Table II. Clinical and bacteriological outcome of children with cholera in the three treatment groups

	Treatment groups					
	Erythromycin (n=15)		TMP-SMX (n=18)		Control (n=15)	
Stool volume (mL/kg body wt.)						
0-24 h (95% CI)	178±96	(125 to 231)	166±177	(78 to 254)	228±160	(139 to 317)
25-48 h	130±100	(75 to 185)	68±65	(36 to 100)	102±90	(52 to 152)
Total stool volume (5 days)	389±249	(251 to 527)	358±279	(219 to 497)	403±314	(229 to 577)
Total ORS intake, mL/kg (mean ±SD)	418±319		379±261		435±537	
Duration of diarrhoea, h	54±26*		53±21*		80±35	
Clinical cure, no. (%)	10 (67)**		15 (82)**		5 (33)	
Bacteriological cure, no. (%)	12 (80)**		15 (83)**		4 (27)	

Erythromycin vs. no-antibiotic *p<0.01 and TMP-SMX vs. no-antibiotic **p<0.001.
Clinical cure was defined as the end of diarrhoea (passage of soft stool) occurring on or before 72 hours without relapse.
Bacteriological cure is defined if the stool culture became negative on day 3 or before after starting treatment and remained negative afterwards.

Of the five clinical failures in the erythromycin group, stools became again less formed from day 4 in one patient and from day 5 in the remaining four patients, and of the three clinical failures in the TMP-SMX group, two improved on day 4 and another on day 5. On the other hand, 10 patients who failed in the control group improved on day 6.

The proportion of patients with *V. cholerae* isolated from stool culture declined from 60% on day 1 post-treatment to 0% on day 5 in the erythromycin group (9/15 and 0/15; CL 32% to 84% and 0% to 22% respectively) compared to 91% on day 1 to 53% on day 5 in the control group (14/15 and 8/15; CL 68% to 100% and 27% to 79% respectively) ($p<0.01$). Similarly, the proportion of patients with *V. cholerae* isolated from stool culture in the TMP-SMX group declined from 94% (17/18; CL 73% to 100%) on day 1 to only 16.7% (3/18; CL 36% to 41%) on day 5 ($p<0.01$) (Fig.). However, these differences in bacteriological response between the erythromycin and TMP-SMX groups were not statistically significant on any day during the treatment.

DISCUSSION

In the present study, patients receiving erythromycin or trimethoprim-sulphamethoxazole showed good clinical and bacteriological cures when compared with a no-antibiotic control. This is in agreement with other clinical studies done previously (6,13-16). However, there was no differences either in clinical or bacteriological cure between the two antibiotic treatment groups. Similarly, the duration of diarrhoea of two antibiotic treatment groups was significantly shorter than the no-antibiotic group. That agrees well with nearly two and half days required in a previous study (13).

Until recently, in this region, the El Tor biotype of *V cholerae* O1 was responsible for epidemics and outbreaks (17). However, the cholera outbreaks that took place during 1987-1989 in southern Bangladesh were mostly caused by *V. cholerae* classical biotype that were tetracycline-resistant (18). *V. cholerae* O1 El Tor biotype strains resistant to tetracycline have since long been reported from other parts of the world. However, only recently similar El Tor biotype of *V. cholerae* O1 has been found to be responsible for epidemics in this region (18,19). In 1988, a cholera epidemic due to *V. cholerae* O1 El Tor biotype was reported from Maharastra, India; 43% of those strains were tetracycline-resistant (20).

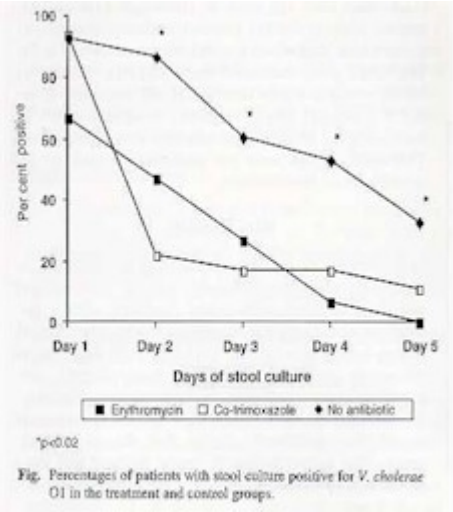

Fig. Percentages of patients with stool culture positive for *V. cholerae* O1 in the treatment and control groups.

In our study, although both the clinical and bacteriological successes were significantly better in children receiving antibiotics compared to the control patients, the volume of stool was similar in all three groups. This may be due to the small number of patients studied in each group.

Nevertheless, our study showed that both erythromycin and trimethoprim-sulphamethoxazole are similarly effective in achieving clinical and bacteriological cure. With the emergence of *V. cholerae* O1 strains resistant to tetracycline and furazolidone, erythromycin and trimethoprim-sulphamethoxazole may serve as effective alternative antimicrobials.

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REFERENCES

1. Khan MU, Eeckels R, Alam AN, Rahman N. Cholera, rotavirus and ETEC diarrhoea: some clinico-epidemiological features. *Trans R Soc Trop Med Hyg* 1988;82:485-8.
2. Lindenbaum J, Greenough WB, III, Islam MR. Antibiotic therapy of cholera. *Bull WHO* 1967;36:871-83.
3. De S, Choudhuri A, Dutta P, Dutta D, De SP, Pal SC. Doxycycline in the treatment of cholera. *Bull WHO* 1976;54:177-9.
4. Wallace CK, Anderson PN, Brown TC, Khanra SR, Lewis GW, Pierce NF, *et al*. Optimal antibiotic therapy in cholera. *Bull WHO* 1968;39:239-45.
5. Alam AN, Alam NH, Ahmed T, Sack DA. Randomised double blind trial of single dose doxycycline for treating cholera in adults. *Br Med J* 1990;300:1619-21.

6. Rabbani GH, Islam MR, Butler T, Shahrier M, Alam K. Single-dose treatment of cholera with furazolidone or tetracycline in a double-blind randomized trial. *Atimicrob Agents Chemother* 1989;33:1447-50.

7. Candau MG. The seventh cholera pandemic. *WHO Chron* 1971;25:155-60.

8. Glass RI, Huq I, Alim ARMA, Yunus M. Emergence of multiply antibiotic-resistance *Vibrio cholerae* El Tor in Bangladesh. *J Infect Dis* 1980;142:939-42.

9. Towner KJ, Pearson NJ, Mhalu FS, O'Grady F. Resistance to antimicrobial agents of *Vibrio cholerae* El Tor strains isolated during the fourth cholera epidemic in the United Republic of Tanzania. *Bull WHO* 1980;58:747-51.

10. Maimone F, Coppo A, Pazzani C, Ismail SO, Guerra R, Procacci P, *et al*. Clonal spread of multiply resistant strains of *Vibrio cholerae* O1 in Somalia. *J Infect Dis* 1986;153:802-3.

11. Finch MJ, Moriss G, Jr., Kaviti J, Kagwanja W, Levine MM. Epidemiology of antimicrobial resistant cholera in Kenya and East Africa. *J Trop Med Hyg* 1988;39:484-90.

12. Molla AM, Sarker SA, Hossain M, Molla A, Greenough WB, III. Rice-powder electrolyte solution as oral therapy in diarrhoea due to *Vibrio cholerae* and *Escherichia coli*. *Lancet* 1982;1:1317-9.

13. Cash RA, Northrup RS, Rahman ASMM. Trimethoprim and sulphamethoxazole in clinical cholera: comparison with tetracycline. *J Infect Dis* 1973;128(suppl):749-53.

14. Gharagozloo RA, Naficy K, Mouin M, Nassirzadeh MH, Yalda R. Comparative trial of tetracycline, chloramphenicol, and trimethoprim sulphamethoxazole in eradication of *Vibrio cholerae* El Tor. *Br Med J* 1970;4:281-2.

15. Uylangco C, Santiago L, Pescante M, Menday P, Christensen O. Pivmecillinam, co-trimoxazole and oral mecillinam in gastroenteritis due to *Vibrio* spp. *J Antimicrob Chemother* 1984;13:171-5.

16. Burans JP, Podgore J, Mansour MM, Farah AH, Abbas S, Abu-Elyazeed R, *et al*. Comparative trial of erythromycin and sulphatrimethoprim in the treatment of tetracycline-resistant *V. cholerae* O1. *Trans R Soc Trop Med Hyg* 1989;83:836-8.

17. Siddique AK, Baqui AH, Eusof A, Haider K, Hossain MA, Bashir I, *et al*. Survival of classic cholera in Bangladesh. *Lancet* 1991;337:1125-7.

18. Siddique AK, Zaman K, Majumder Y, Islam Q, Bashir I, Mutsuddy P, *et al*. Simultaneous outbreaks of contrasting drug resistant classic and El Tor *Vibrio cholerae* O1 in Bangladesh (letter). *Lancet* 1989;2:396.

19. Thretall EJ, Rowe B, Huq I. Plasmid-encoded multiple antibiotic resistance in *Vibrio cholerae* El Tor from Bangladesh. *Lancet* 1980;1:1247-8.

20. Fule RP, Powar RM, Menon S, Basutkar SH, Saoji AM. Cholera epidemic in Solapur during July-August, 1988. *Indian J Med Res* 1990;91:24-6.

21. Bhattacharya SK, Bhattacharya MK, Dutta P, Dutta D, De SP, Sikder SN, *et al*. Double-blind, randomized, controlled clinical trial of norfloxacin for cholera. *Antimicrob Agents Chemother* 1990;34:939-40.

22. Irgham B, Brentnal DW, Dale EA, McFadzean JA. Arthropathy induced by antibacterial fused N-alkyl-4-pyridone-3-carboxylic acids. *Toxicol Lett* 1977;1:21-6.