COMPARISON OF THE EFFICACY OF TETRACYCLINE AND NORFLOXACIN IN THE TREATMENT OF ACUTE SEVERE WATERY DIARRHEA

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Abstract. Antibiotic treatment appears to shorten the duration of diarrhea and eradicate *Vibrio cholerae*. The objective of this study was to compare the efficacy of tetracycline with norfloxacin therapy in patients (adults and children) with acute severe watery diarrhea caused by VC 01and VC 0139. Patients (adults and children) with acute severe watery diarrhea admitted to Bamrasnaradura Infectious Disease Hospital, Thailand were randomized to receive either tetracycline (500 mg qid in adults and 12.5 mg/kg qid in children) or norfloxacin (400 mg bid in adults and 7.5 mg/kg bid in children) for 3 days each. The duration of diarrhea and the fecal shedding were comparable between two groups. Thirteen cases were treated with tetracycline and twelve cases with norfloxacin. The results showed the mean duration of diarrhea in tetracycline-treated and norfloxacin-treated groups were 1.31 and 1.25 days, respectively. The mean fecal shedding in tetracycline-treated and norfloxacin-treated group were 1.38 and 1.33 days, respectively. However, there were no statistically significant differences between two groups of both comparisons ($p > 0.05$). All isolates (VC 01 and VC 0139) in this study were susceptible to both antibiotics. Tetracycline therapy is as good as norfloxacin therapy for quick recovery and time for bacterial eradication in patients with acute severe watery diarrhea caused by *Vibrio cholerae*. Children aged less than 8 years should not use tetracycline therapy because of its toxic effects.

INTRODUCTION

There are many enteropathogens that have been reported as causes of acute severe watery diarrhea, such as *Vibrio clolerae* (Dhar *et al*, 1996), non-typhoidal *Salmonella* (Moolasart *et al*, 1997) and rotavius (Timenetsky *et al*, 1996). *Vibrio cholerae* has been recognized as the most common cause of acute severe watery diarrhea and often remains epidemic in developing countries (Faruque *et al*, 1996; Sachdeva *et al*, 1995; Morris and the Cholera Laboratory Task Force, 1994). Acute rice water diarrhea is the most presenting symptom of disease. The type of diarrhea is usually severe and can lead to rapid dehydration, acidosis and collapse. Death may occur in a few hours if patients are left untreated.

Before 1992, *Vibrio cholerae* in group O1 (VC O1) were commonly responsible for acute severe watery diarrhea. In late 1992 and early 1993, *Vibrio cholerae* 0139 (VC 0139), one of the VC non-01 strains caused outbreaks of cholera-like diarrhea in India and Bangladesh (Faruque *et al*, 1996; Shimada *et al*, 1993).

Therapy for acute severe cholera diarrheal disease includes: rapid replacement of water and lost salts in appropriate amounts, plus concentration and antimicrobial therapy to shorten the duration of diarrhea and thereby reduce fluid loss in both VC O1 and VC 0139 cases. Both cholera strains have been reported to be susceptible to tetracycline and norfloxacin, a fluoroquinolone (Albert *et al*, 1993; ICDDR, B, 1993; Greenough III, 1995; Amin *et al*, 1995; Dutta *et al*, 1996).

We conducted a comparative study of the efficacy of tetracycline with norfloxacin in the treatment of acute severe watery diarrhea caused by VC O1 and VC 0139 at Bamrasnaradura Infectious Disease Hospital where the first cases of VC 0139 were found in Thailand (Chongsa-Nguan *et al*, 1993) in the 3 year period (January 1994 to December 1996).

MATERIALS AND METHODS

Study population

The study was conducted at Bamrasnaradura Infectious Disease Hospital during January 1994-

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December 1996. Patients (adults and children) with acute severe watery diarrhea seen and admitted to the hospital were divided into two groups by randomized treating with tetracycline (500 mg qid in adults and 12.5 mg/kg qid in children) and norfloxacin (400 mg bid in adults and 7.5 mg/kg bid in children) for 3 days each. Their clinical history for diarrhea and physical examination results were recorded. All subjects reporting chronic or intermittent diarrhea, underweight or malnutrition, low immunity or receiving medication within a week prior entering the hospital were excluded from the study.

Acute severe watery diarrhea was defined as at least three watery stools during 24 hours or two watery stools within 8 hours in the presence of moderate to severe dehydration.

Isolation and identification of VC 01 and VC 0139

The stool specimens collected from these patients were inoculated into the alkaline peptone water (APW) media, and subcultured onto the thiosulphate citrate bile salt (TCBS). Suspected colonies were tested biochemically according to standard methods. Serotyping with polyvalent antisera was done on the isolated VC strains. VC non-01 strains were serotyped and VC 0139 were detected by specific 0139 antisera. The stool specimens of patients were repeatedly isolated every day until a negative result occurred for 2 consecutive days.

Antimicrobial susceptibility

Antibiotic sensitivity testing was done by the agar disk diffusion method (National Committee for Clinical Laboratory Standards, 1984).

Statistical methods

The statistical significance of differences between clinical success and bacteriological success in the number of days for clinical resolution and disappearance of VC in stool, were calculated by using unpaired *t*-test.

RESULTS

Base-line characteristics

During the 3-year study (1994-1996), a total of 60 stool specimens were collected from patients with acute severe watery diarrhea seen in this hospital. Thirty-five cases (12 cases with negative result for VC 01 or VC 0139 and 23 cases with incomplete follow-up data) were excluded. Twenty-five cases were included in the final analysis, of which thirteen cases (11 adults and 2 children) were treated with tetracycline and twelve cases (9 adults and 3 children) with norfloxacin. The patients of both groups were infected with both VC 01 and VC 0139. VC 01 was dominant cholera strain and VC 0139 was found only during January-March 1994.

The base-line characteristics of patients in both groups were almost similar on admission (Table 1).

Table 1

Base-line characteristics of patients with acute severe watery diarrhea according to treatment group.

	Tetracycline group (N = 13)	Norfloxacin group (N = 12)
Age average (years)	35.2	38.8
range (years)	1-80	1 1/2-79
Adult : children	11 : 2	9 : 3
Male : Female	7 : 6	6 : 6
Clinical features - Fever	2	1
- Vomiting	6	7
- Abdominal pain	4	4
Frequency of stool 5-10/day	8	9
VC 01/VC 0139	9/4	7/5

Table 2

Patient outcome according to the treatment of acute severe watery diarrhea performed.

	Tetracycline group (N = 13)	Norfloxacin group (N = 12)	p-value
Clinical success (days)	1.31	1.25	> 0.05
range (days)	1-2	1-2	
Bacteriological success (days)	1.38	1.33	> 0.05
range (days)	1-3	1-3	

The patients of both groups had acute severe watery stool with moderate to severe dehydration and were admitted to the hospital.

Comparative results of treatment for patients with acute severe watery diarrhea are shown in Table 2. Clinical success of patients in the tetracycline-treated group and the norfloxacin-treated group was observed in 1.31 and 1.25 days respectively. Bacteriological success in the tetracycline-treated group and the norfloxacin-treated group was observed in 1.38 and 1.33 days respectively. However, there was no statistically significant difference between the two groups in both comparisons ($p > 0.05$). All isolates in this study were susceptible to tetracycline and norfloxacin. There were no complications after treatment with both antibiotics, even in children. There was no patient death during this study.

DISCUSSION

Vibrio cholerae 01 and 0139 Bengal remain important causes of acute severe watery diarrhea both in adults and children (Amin *et al*, 1995; Albert *et al*, 1996). Our study produced similar results. In the 3 year period (1994-1996) of our study, VC 01 was still dominant cholera strain and VC 0139 was found only in January-April, 1994. The prevalence of VC 0139 decreased dramatically after this strain had emerged for one year and was similar to the prevalence in Dhaka. The factor(s) contributing to the dramatic decline in prevalence of VC 0139 is (are) not well understood (Faruque *et al*, 1996). Clinical symptoms of VC 01 and VC 0139 were similar and difficult to differentiate. Both cholera strains differ in their antimicrobial susceptibility patterns (Dhar *et al*, 1996). Thus, a choice of appropriate antibiotics that can eradicate both cholera strains is necessary for the quick recovery of patients. Tetracycline and quinolones have been drugs of choice as they effective for both cholera strains (Greenough, 1995; Amin *et al*, 1995). Although the tetracycline-resistant strain of VC 01 was reported in previous study (Olukoya *et al*, 1995), it was not found in our study. Our data showed the efficacy of norfloxacin was better than tetracycline in clinical improvement (1.25 *vs* 1.31 days) and bacterial eradication (1.33 *vs* 1.38 days) but there were no statistically significant differences in both comparisons ($p > 0.05$).

When considering the selection of antibiotics for children, it is important to acknowledge the arthropathogenic effect of fluoroquinolones in young animals. This has led to the decision not to use them in children and adolescents, despite the fact that the significance of the effect on humans is still unclear (Stahlmann, 1990). Recent studies in England and Canada suggested the safety of the new quinolones including norfloxacin, in pregnancy and children (Berkovitch *et al*, 1994; Wilton *et al*, 1996). Thus, norfloxacin can be safely used in children with acute severe cholera diarrheal disease. Tetracycline should not be used in children aged less than 8 years because of its toxic effect to teeth and bones (Anonymous, 1977).

In conclusion, tetracycline therapy is as good as norfloxacin therapy in the treatment of acute severe watery diarrhea caused by *Vibrio cholerae*. Norfloxacin should be the preferred choice for children, however, an effective vaccine for both cholera starins is needed.

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