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Single-Dose Doxycycline for Cholera

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To determine the efficacy of single-dose doxycycline in the treatment of cholera, we carried out a randomized prospective trial in 65 patients. Treatment consisted of either a single dose of 200 mg of doxycycline (or 4 mg/kg in patients less than 15 years old) or multiple doses of doxycycline, 500 mg over 4 days (or 10 mg/kg in patients less than 15 years old). There were no differences between the groups in the volumes of intravenous fluid required, volumes of diarrheal stool, or durations of diarrhea. The mean duration of positive stool cultures for *Vibrio cholerae* was similar for the two groups, although in both groups several patients continued to excrete Vibrios in the stool for more than 3 days. Blood levels of antibiotic demonstrated that the doxycycline was absorbed in spite of the rapid transit time associated with severe diarrhea. These results suggest that although tetracycline remains the drug of choice for cholera, doxycycline is a reasonable alternative, and that a single dose of 200 mg (4 mg/kg in children) is effective clinically.

The treatment of cholera has been improved and simplified in recent years. These improvements include the use of standardized intravenous and/or oral solutions for rehydration and hydration maintenance, coupled with antibiotics which decrease the volume and duration of diarrhea. These measures allow health workers to treat cholera inexpensively and with virtually complete success. Tetracycline is the antibiotic of choice (4, 7). Doxycycline, a long-acting tetracycline, has, however, been shown to be equally effective when given for 4 days (6). More recently, shorter courses of doxycycline have been used successfully for cholera, including a single dose of 200 or 300 mg given on the first day of illness (2). A single-dose therapy has many advantages, one of which would be to eliminate problems of patient compliance. It would also simplify logistics in treating hospitalized patients during an epidemic, since no further antibiotic would need to be given after the initial dose.

Since doxycycline may cause a dose-related side effect of nausea and vomiting, we felt that 200 mg in a single dose was the maximal dose that would be tolerated by all patients with severe diarrhea, many of whom are vomiting already. The present study was designed to compare the effectiveness of a single 200-mg dose of doxycycline with a 4-day multiple dose course of the same drug, using a regiment that has previously been shown to be equally effective with tetracycline (6) in a group of actively purging patients with cholera.

MATERIALS AND METHODS

Male patients, aged 5 to 50 years, who visited the Cholera Research Hospital, Dacca, Bangladesh with a clinical history of acute watery diarrhea, evidence of ≥5% dehydration, and a stool dark-field examination positive for *Vibrio cholerae*, and who continued to purge following admission, were eligible for the study. Patients who had taken antibiotics within 1 week of hospitalization were excluded from the study, as were patients who had dual infections with two or more bacterial pathogens. The study was explained to all patients, and informed written consent was obtained from the patient, or from the parents in the case of children.

All patients were weighed, placed on cholera cots, and clinically examined, noting especially the signs of dehydration. A catheterized stool specimen was obtained for microscopic examination and for culture. The patients were rehydrated within 2 to 4 h using standard intravenous therapy (1) and were maintained on intravenous maintenance hydration. Food and water were allowed as soon as the patient tolerated this.

Patients were assigned to either a single-dose or multiple-dose doxycycline regimen according to a predetermined list of random numbers. Patients receiving a single dose were given 200 mg of doxycycline (or 4 mg/kg if aged less than 15 years) after rehydration, within 2 to 4 h of admission and after some food had been taken. Patients receiving multiple-dose therapy received 100 mg of doxycycline (or 2 mg/kg if less than 15 years of age) in a similar manner; this same dose was then repeated after 12 h, and then daily for 3 days.

Fluid intake and output measurements were recorded every 8 h. Rectal swab cultures were obtained daily for the duration of the hospitalization. Patients remained in the hospital until their diarrhea had ceased for at least 24 h and their fecal culture was

negative for 2 consecutive days. Diarrheal stool was defined as loose or watery stool which could be poured from the bucket for measuring.

All fecal cultures were plated immediately onto MacConkey, *Salmonella-Shigella*, and Monsur agar plates and were also inoculated in taurocholate tellurite peptone water for 6 h for subsequent plating onto a second Monsur agar plate (5). Bacteria from colonies typical of *V. Cholerae* were tested for agglutination with polyvalent O group 1 and specific antisera and were tested for hemagglutinating activity with chicken erythrocytes.

Serum was obtained from 24 patients for the measurement of doxycycline serum levels. These were obtained 2 h after the first dose in both treatment groups, and 18 to 24 h after the first dose in the single-dose group. Five patients who received a single dose and whose level was measured on the day of admission were again given 200 mg on day 5 (the day of discharge for these patients) after their diarrhea had ceased; blood was again obtained 2 h after taking the drug. Serum levels were determined by the microbiology laboratory at Pfizer Laboratory.

RESULTS

Seventy-four patients were initially admitted into the study. Nine were eliminated for one of the following reasons: stool culture revealed *Shigella* in addition to *V. cholerae* (two), stool culture failed to confirm diagnosis of cholera (three), patient absconded (two), error in dosage of doxycycline (two). Of the 65 patients with bacteriologically confirmed cholera (El Tor) who completed the study, 36 received single-dose doxycycline and 29 received multiple doses of doxycycline. The two groups were similar in regard to mean age, dehydration, duration of diarrhea prior to hospitalization, and admission white blood count as shown in Table 1.

Patients were able to take the doxycycline without difficulty soon after initial hydration and after some food was taken. Three patients who were given the drug before taking food vomited the medication, and in these cases the doxycycline was administered again.

Patients in the two groups required similar mean volumes of intravenous fluid and purged similar mean volumes of stool, as shown in Table 2. In both groups most of the total diarrheal stool was passed during the first 24 h, and in both groups more than 90% of the intravenous fluid was given during the first 24 h.

The results of stool cultures are also shown in Table 2. Although the mean duration of *Vibrio*-positive stool culture was approximately 2 days in both groups, 9 of 36 (25%) patients in the single-dose group and 4 of 29 (14%) in the multiple-dose group continued to have *V. cholerae* isolated from stool specimens for more than 3 days. Those patients with a positive culture on day 4 were treated with tetracycline, 4 g over 2 days, and discharged.

Doxycycline was absorbed during active purging, as indicated by blood levels of the drug. All of 12 patients in the single-dose group and 10 of 12 patients in the multiple-dose group had detectable levels of doxycycline in the serum 2 h after the first dose of antibiotic, with a mean level of 1.9 μg/ml (range 0.8 to 3.5) and 0.78

TABLE 1. *Comparison of patients receiving either single-dose or multiple-dose doxycycline*

Dose	Parameters[a]			
	Age (years)	Duration of diarrhea prior to admission (h)	Weight gain during hospitalization (%)	Admission white blood count
Single	22 ± 3	12 ± 2	8.2 ± 0.4	20,300 ± 1,200
Multiple	25 ± 3	13 ± 2	8.0 ± 0.5	16,600 ± 900

[a] Mean ± standard error.

TABLE 2. *Intravenous fluid requirements, stool volumes, and stool culture results in patients with cholera receiving either single-dose or multiple-dose doxycycline*

Dose	Intravenous fluid requirements (ml/kg)[a]			Mean duration of therapy (h)
	Total	During first 24 h	Total maintenance	
Single	210 ± 22	190 ± 15	130 ± 22	26
Multiple	230 ± 22	210 ± 10	154 ± 22	26

Dose	Diarrheal stool (mg/kg)[a]		Duration of diarrhea (h)		Mean duration of positive stool culture for *V. cholerae* (days)
	Total	During first 24 h	After hospitalization	Of output >1 mg/kg per h	
Single	130 ± 20	100 ± 8	33	26	2.3
Multiple	140 ± 19	130 ± 15	33	26	2.0

[a] Mean ± standard error.

μg/ml (range 0.2 to 1.9), respectively. The level at 18 to 24 h in the single-dose group was unchanged with a mean of 1.9 μg/ml (range 0.1 to 4.7). Five of the patients who received single-dose therapy during active cholera were again given 200 mg of doxycycline on day 5 after diarrhea had stopped. The mean 2-h blood level of these five patients during diarrhea had been 2.1 μg/ml (range 1.0 to 3.5 μg/ml), and on day 5 it was 3.2 μg/ml (range 2.2 to 4.0 μg/ml) ($P > 0.1$ by paired t test).

DISCUSSION

Tetracycline remains the drug of choice in the treatment of cholera since it shortens the duration of diarrhea and eliminates the *Vibrio* from the stool within 1 to 2 days. Doxycycline is equally effective clinically in lessening the diarrhea; the duration of excretion of the *Vibrio*, however, is not as effectively shortened as with tetracycline therapy. Whether these asymptomatic culture-positive patients represent a significant public health risk to the community is not clear, especially since the hospitalized and treated cholera patients may represent only a small fraction of the total number of people infected with and excreting *V. cholerae* during a cholera epidemic (8). Nevertheless, it would seem reasonable to use a drug that was maximally effective both clinically and bacteriologically under optimal treatment conditions.

There are situations, however, where doxycycline may be appropriate, especially where supervision of patients, by necessity, is minimal, such as in outpatient clinics and rehydration centers. When using a single dose of doxycycline, the practitioner can ensure that the patient has taken his full course of therapy, and does not have to rely on patient compliance to complete the therapy. Doxycycline is also indicated in patients in whom renal failure is a potential complication and in whom toxic levels of antibiotic might accumulate if tetracycline were used.

This study has shown that doxycycline is well absorbed in spite of active watery diarrhea with the associated rapid transit time. Serum levels 2 h after a 200-mg oral dose in normal subjects average 3 μg/ml, which is comparable to the levels seen in our patients with cholera (3).

Although antibiotics shorten the diarrhea, maintenance of hydration with intravenous and/or oral fluid therapy remains the primary mode of therapy, and no antibiotics can replace the need for careful attention to the status of hydration in patients with severe watery diarrhea.

Since single-dose doxycycline is effective in the treatment of cholera, it might also be expected to be useful in treating other watery diarrheal diseases such as those due to enterotoxigenic *Escherichia coli*. Future studies will be necessary to establish its efficacy in the treatment of this disease.

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