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Single-Dose Treatment of Cholera with Furazolidone or Tetracycline in a Double-Blind Randomized Trial

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To evaluate single doses of 400 mg of furazolidone and 1 g of tetracycline given orally to patients with diarrhea due to *Vibrio cholerae*, we studied 87 adults in a randomized, double-blind, placebo-controlled trial. All patients received intravenous fluids for rehydration and no other drugs. The total volumes of stool (mean ± standard deviation) during a 6-day period after treatment were significantly smaller in the tetracycline group (10.5 ± 8.6 liters) than in the furazolidone group (20.9 ± 15.9 liters) and the placebo group (19.1 ± 10.5 liters) ($P < 0.01$). The duration of diarrhea and volumes of intravenous fluids were also significantly reduced in the tetracycline group ($P < 0.05$). However, there were no differences between the furazolidone and the placebo groups with regard to stool volume, intravenous fluid, and duration of diarrhea. Within 48 h of treatment, tetracycline significantly reduced the number of patients with positive stool cultures for *V. cholerae* (37%) compared with furazolidone treatment (96%) and the placebo (97%) ($P < 0.001$). Although the tetracycline group had a significantly higher incidence (61%) of bacteriologic relapse (negative stool cultures on days 2 and 3, followed by positive cultures afterward) compared with that in the furazolidone group (40%) and the placebo group (33%), this was not associated with clinical relapse. There were no differences between the furazolidone and placebo groups with regard to any of the bacteriologic responses examined. These data indicate that a single dose of 1 g of tetracycline is effective in the treatment of cholera, but it is associated with asymptomatic bacteriologic relapse. A single dose of 400 mg of furazolidone is not therapeutically effective in cholera.

Cholera is one of the most severe forms of infectious diarrheas, characterized by vomiting, dehydration, shock, and acidosis with a sometimes fatal outcome (17, 24). It has been shown that antibiotics given concurrently with fluid and electrolyte replacement significantly reduce the volume and duration of diarrhea and the period of *Vibrio cholerae* excretion in the feces (2, 7). Many antimicrobial agents, including tetracycline, chloramphenicol, doxycycline, and furazolidone, have been shown to be clinically useful when prescribed in a standard dosage for several days (2–5, 7, 10, 12, 13, 16, 19, 21). Although conventional dosages of tetracycline (2 to 4 g for 3 to 5 days) have long been recognized as the treatment of choice in cholera (20), the drug cannot be prescribed to pregnant women and young children because of the adverse effects of tetracycline on teeth and growing bones (8, 23). Some tetracycline-resistant strains of *V. cholerae* have recently been isolated (6, 14), but antibiotic resistance has not become a widespread problem.

Furazolidone, a nitrofuran derivative, can be a useful alternative to tetracycline because furazolidone has been shown to be clinically useful in cholera when given for several days (3, 4, 10, 11, 16). Unlike tetracycline, furazolidone is not well absorbed from the intestine, and systemic effects are rare. Bacterial resistance to furazolidone develops slowly. Although shorter courses of low-dose antibiotics have been tried in cholera, a well-controlled study comparing single doses of these drugs has not been reported. Single-dose treatments minimize cost and ensure safety and compliance of patients and are especially important during epidemics. In this study we compared the therapeutic effects of single doses of tetracycline and furazolidone in adult patients with cholera.

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MATERIALS AND METHODS

Patient selection. The study was carried out at the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh. Eligible for the study were adult men and women (15 years and above) who visited the treatment center with (i) a history of acute watery diarrhea for less than 24 h, (ii) clinical evidence of loss of body weight (5% or more) due to dehydration, and (iii) stools that were dark field positive for *V. cholerae*. Patients who had taken antibiotics within 1 week of admission were excluded from the study, as were patients who were severely malnourished or pregnant. The study procedures were explained to patients, and their informed, written consents were obtained before allocation to treatment. The study protocol was approved by the institutional Ethical Review Committee.

Clinical management. After recording the body weight, we placed the patients on cholera cots and performed a clinical examination, specifically noting signs of dehydration. A catheterized stool specimen was obtained for microscopic and bacteriologic examination. Within 2 to 4 h of admission, we rehydrated patients with an intravenous (i.v.) solution containing 133 mmol of sodium per liter, 13 mmol of potassium per liter, 98 mmol of chloride per liter, and 48 mmol of acetate per liter. The volume of i.v. fluid given was 5 to 7% of the body weight initially and was followed by quantitative replacement of all liquid stool passed in the hospital. All liquid stool, urine, and vomitus were separately collected and quantitated at 8-h intervals. The progress of rehydration was assessed by determining the changes in the body weight, blood pressure, character of radial pulse, skin turgor, and urine volume. The volume of i.v. fluid infused, vital signs, and volumes of stool and urine were recorded every 8 h,

TABLE 1. Clinical characteristics of cholera patients before allocation to treatment

Treatment group (*n*)	Age[a] (yr)	Body wt[a] (kg) on:			Stool vol[a] (liters)[b]	h of diarrhea[a]	No. (%) of *V. cholerae* isolates susceptible to:	
		Admission	Day 3	Day 7			Tetracycline	Furazolidone
Tetracycline (30)	28 ± 11	42.1 ± 8.0	43.4 ± 7.5	43.0 ± 7.7	1.8 ± 0.6	10.2 ± 4.1	26 (87)	21 (70)
Furazolidone (27)	33 ± 12	41.5 ± 4.9	43.0 ± 5.0	42.2 ± 5.2	2.1 ± 0.9	12.6 ± 3.8	26 (96)	21 (78)
Placebo (30)	31 ± 12	39.9 ± 5.9	41.2 ± 5.5	40.5 ± 5.7	2.1 ± 1.5	13.1 ± 4.6	25 (83)	24 (80)

[a] Data are given as means ± standard deviations.
[b] Stool volume during the first 6 h after admission.

beginning at the time of admission and continuing until the diarrhea stopped. Intake and output measurements of fluids were made to the nearest 5 ml. Participating patients remained in the hospital for 7 days or until they had stopped excreting *V. cholerae* for at least 3 consecutive days and had passed a formed stool. Food and water were allowed as soon as they were tolerated.

Randomization and treatment allocation. Patients who purged ≥20 ml/kg of body weight during the 6 h after admission were randomly allocated to treatment with furazolidone, tetracycline, or placebo by using a table of random numbers. Bottles containing the drugs and placebo were numerically coded and provided by Norwich Eaton Pharmaceuticals, Inc., Norwich, N.Y. The code list was kept in New York and opened only after the study had been completed. On the first hospital day, each of 27 patients was given 400 mg of furazolidone as two capsules of 200 mg each, 30 patients were given 1 g of tetracycline hydrochloride as two capsules of 500 mg each, and 30 patients were given identical placebo capsules. The justification for including a placebo group is that cholera is a self-limited disease that produces no structural damage to the intestine; replacement of lost intestinal fluid in adequate quantities results in complete recovery.

Bacteriologic procedures. Rectal swab specimens were taken from patients before starting treatment and then every day for 7 days for isolating enteric pathogens. Fecal specimens were plated immediately onto MacConkey, salmonella-shigella, and Monsur (taurocholate tellurite gelatin) agar plates and were also inoculated into taurocholate tellurite peptone water for 6 h of enrichment and subsequent plating onto a second Monsur agar plate (15). Bacteria from colonies typical of *V. cholerae* were tested for agglutination with polyvalent O group 1 antiserum. The susceptibility of all *V. cholerae* isolates to tetracycline and furazolidone was tested by the Bauer-Kirby method with in vitro antibiotic disks (1). In the evening of day 6, purging was induced by magnesium sulfate given orally (5 g), and stool specimens were collected the next day.

Definition of outcome variables. Diarrhea was defined as liquid (watery) stools that can be quantitated by transferring into a measuring flask to the nearest 5 ml. The primary indicators of treatment effect in this study were (i) posttreatment stool and i.v. fluid volumes in liters, (ii) duration of diarrhea in hours, and (iii) duration of vibrio excretion in hours. Duration of diarrhea was defined as the time elapsed from entry until the end of diarrhea. The end of diarrhea was defined as the end of the last 8-h period in which a liquid stool was passed. Clinical success was defined as the end of diarrhea occurring on or before day 4 without subsequent relapse, and clinical failure was defined as diarrhea continuing past day 4. Day 4 was selected as the cutoff time because studies of tetracycline in cholera indicated that most treated patients ceased having diarrhea within 2 to 4 days after starting treatment (2, 7, 20, 21). If there was cessation of diarrhea on or before day 4 and for 1 day or longer, followed by return of diarrhea, it was considered a clinical relapse. Bacteriologic failure was defined as stool cultures that were positive on days 2, 3, and 4 after treatment, and bacteriologic success was defined as cultures that were negative on 3 consecutive days starting on day 4 or earlier with negative cultures after magnesium sulfate purging on day 7. When cultures were negative on days 2 or 3, followed by positive cultures after that, the case was considered a bacteriologic relapse. Negative cultures on 3 consecutive days starting on day 4 or earlier with positive cultures after purging indicated that the patient was a bacteriologic carrier (22). The outcome variables were statistically compared among different treatment groups by using analysis of variance and chi-square significance tests.

RESULTS

Clinical characteristics. Initially 114 patients were entered into the study. Twenty-seven were eliminated for one of the following reasons: (i) stool culture failed to confirm diagnosis of cholera (17 patients), (ii) departure before completion of study (6 patients), and (iii) coinfection with another pathogen (4 patients). Of the 87 patients with bacteriologically confirmed cholera who completed the study, 27 received furazolidone, 30 received tetracycline, and 30 received placebo. Patients in the three treatment groups were similar with regard to age, dehydration status, duration of diarrhea before admission, body weight, and base-line purging rates (Table 1). Throughout the study period, i.v. rehydration restored the fluid deficit adequately, as indicated by an increase in body weight, urine output, and improvement of clinical vital signs.

Reduction of stool and i.v. fluid volumes. During the first and second 48 h after treatment, tetracycline-treated patients had a significantly lower mean stool volume compared with those treated with furazolidone and placebo ($P < 0.01$) (Fig. 1). However, there was no difference in mean stool volumes of patients treated with furazolidone or placebo during the same periods. After treatment, the mean cumulative stool volume over the 6-day period of illness was significantly less in the tetracycline group than in the furazolidone or placebo group ($P < 0.01$). In all three groups, most of the total diarrheal stool was passed during the first 48 h. Thereafter, diarrhea gradually declined to insignificant levels, and no differences were seen in stool volumes during the third 48 h among the groups.

The volumes of i.v. fluid infused during each time period closely matched the corresponding stool volumes in each of the three treatment groups. The total amounts of i.v. fluid required (mean ± standard deviation) were significantly less in the tetracycline group (11.6 ± 9.6 liters) compared with those in the furazolidone (22.1 ± 16.5 liters) and placebo

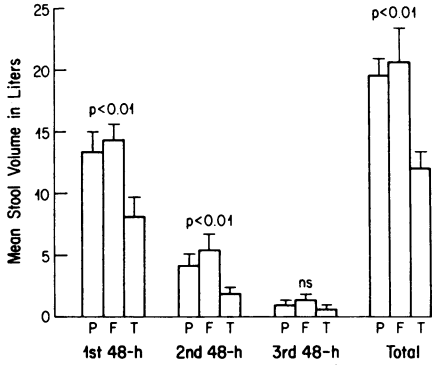

FIG. 1. Stool volumes measured at 8-h intervals after administration of drugs or placebo. Total represents mean cumulative stool volumes over three 48-h periods. Brackets show standard errors of the means. Abbreviations: P, placebo (n = 30); F, furazolidone (n = 27); T, tetracycline (n = 30); ns, statistically not significant. P values were calculated by analysis of variance.

(19.9 ± 11.4 liters) groups ($P < 0.01$). However, there was no significant difference between the furazolidone and placebo groups with respect to i.v. fluid volume.

Duration of diarrhea. The duration of diarrhea (hours, mean ± standard deviation) in the tetracycline group was 40.9 ± 32.7 h, which was significantly shorter than 73.9 ± 33.3 and 80.7 ± 30.9 h in the furazolidone and placebo groups, respectively ($P < 0.05$). However, the duration of diarrhea in the furazolidone group did not differ significantly from that in the placebo group.

Clinical response. According to the definitions, there were significantly more clinical successes in the tetracycline group compared with the furazolidone and placebo groups (Table 2). Although the tetracycline group had slightly higher clinical relapse rates than the furazolidone and placebo groups, it was not statistically significant ($P > 0.05$). Clinical success and failure rates in the furazolidone group were not significantly different from those in the placebo group ($P > 0.05$). No side effects of the drugs were detected by questioning patients daily about symptoms and examining them routinely.

Bacteriologic response. Tetracycline treatment resulted in significantly fewer patients with positive stool cultures during the first 48 h compared with results of furazolidone and placebo treatments ($P < 0.001$) (Table 3). During the second and third 48-h posttreatment periods, culture-positive patients were fewer in the tetracycline group than in the furazolidone group ($P < 0.05$). However, after 3 days, a significantly larger proportion of patients relapsed in the tetracycline group (61%) compared with the furazolidone (40%) and placebo (33%) groups ($P < 0.05$). When furazolidone and placebo groups were compared, no statistically significant differences were found in any of the defined bacteriologic criteria examined.

TABLE 2. Clinical outcomes of cholera patients treated with single doses of tetracycline, furazolidone, and placebo[a]

Treatment group (n)	% of patients with the following outcome:		
	Success	Failure	Relapse
Tetracycline (30)	83[b]	10	7
Furazolidone (27)	56	41	4
Placebo (30)	57	43	0

[a] For definitions of outcomes, see Materials and Methods.
[b] The rate of clinical success was significantly greater for tetracycline when compared separately with that of furazolidone and placebo by chi-square tests ($P < 0.025$).

TABLE 3. Results of stool cultures for *V. cholerae* in patients after treatment with tetracycline, furazolidone, and placebo

Treatment group (n)	% of patients with positive stool cultures at ends of consecutive 48-h periods after treatment		
	1	2	3
Tetracycline (30)	37[a]	46[b]	0[b]
Furazolidone (27)	96	74	15
Placebo (30)	97	63	13

[a] The rate of positive stool cultures was significantly lower after 48 h in patients treated with tetracycline than that in patients receiving furazolidone or placebo by the Fisher exact test ($P < 0.001$).
[b] The rates of positive stool cultures in patients treated with tetracycline were significantly lower than those in patients treated with furazolidone at end of the second 48-h period ($P < 0.05$ by the chi-square test) and at end of the third 48-h period ($P < 0.05$ by the Fishers exact test).

Six patients in the furazolidone group were infected with furazolidone-resistant *V. cholerae*, and four patients in the tetracycline group were infected with tetracycline-resistant organisms. Antimicrobial drug resistance correlated with greater mean total stool volumes in patients with resistant organisms compared with those infected with susceptible ones (30.0 versus 18.0 liters in the furazolidone group and 16.5 versus 9.5 liters in the tetracycline group), but these differences were not statistically significant ($P > 0.05$).

DISCUSSION

Tetracycline has long been recognized as the drug of choice in the treatment of cholera because of its beneficial clinical and bacteriologic effects. Although we did not include a multiple-dose group in our study, it appears that a single-dose of 1 g of tetracycline produced a magnitude of clinical and bacteriological improvement similar to that seen in patients conventionally treated with multiple doses of tetracycline or other antibiotics to which the infecting vibrios are susceptible (2–5, 7, 10, 12, 13, 16, 19–21). Similar observations were reported with a single dose of doxycycline and a single dose of tetracycline (1 and 2 g) in comparable groups of cholera patients (9, 18, 19).

Although tetracycline treatment significantly reduced the clinical failures, some clinical relapses occurred in the tetracycline (7%), furazolidone (4%), and placebo (0%) groups. These differences, however, were not statistically significant. Similar clinical relapse rates (3 to 5%) were reported in a group of comparable patients treated with larger dosages of tetracycline for 2 to 4 days (2). It has been shown that increasing the dosage of tetracycline 2 to 3 times from the standard therapeutic dosage did not appear to enhance its therapeutic action. Therapeutic failures occurred in patients treated with a 1-day regimen as well as in those treated with 4-day regimens (2, 12).

In our study, a single-dose of 1 g tetracycline was associated with an undesirably high incidence of bacteriologic relapse (61%). That this was related to treatment is indicated by a significantly lower rate of relapse in the untreated controls (33%). Higher incidences of bacteriologic relapse and prolonged fecal excretion of vibrios had been reported in patients treated with abbreviated courses of antibiotics (9, 12, 13). In contrast, large doses of tetracycline given over a more extended period (1 g daily for a week or 500 mg every

6 h for 48 h) were not associated with bacteriologic relapse at all (7, 16, 20). These findings indicate that short courses of low-dose antibiotics tend to suppress the growth of vibrios in the gut rather than eradicating them. In our study, bacteriologic relapses were not associated with clinical relapse. Thus, the significance of bacteriologic relapse is related to its potential public health implications, particularly the secondary spread in the environment. However, long-term carriers are rare in cholera, and this consideration should not deter public health practitioners from using antimicrobial treatment for achieving a clinical cure (22).

In our study, a single dose of 400 mg of furazolidone was not effective because the clinical and bacteriologic responses were similar to those of placebo. However, larger doses of furazolidone (1.2 to 2.4 g) given over 2 or 3 days have been shown to produce clinical improvement comparable to those with conventional dosages of tetracycline but were not effective bacteriologically (11, 16). Patients treated with furazolidone excreted vibrios longer than did those on tetracycline (16). Similar findings were reported in cholera patients given 1,200 mg of furazolidone for 3 days (4). The lack of effect of a single dose of furazolidone may be related to the insufficient luminal concentration of the drug, since it has been shown that, in vitro, higher concentrations of furazolidone than tetracycline are required to inhibit the growth of *V. cholerae* (16). Similar concentrations may not be attainable in the intestine due to increased transit time in cholera. Unlike tetracycline, furazolidone is poorly absorbed, and there is no reexcretion of the drug into the intestine from the enterohepatic circulation.

Of the 87 patients, there were 10 with tetracycline-resistant organisms and 12 with furazolidone-resistant organisms. There were 4 patients in the tetracycline group infected with tetracycline-resistant organisms and 6 patients in the furazolidone group infected with furazolidone-resistant organisms; these 10 patients produced greater quantities of stool than did patients infected with susceptible organisms. Although it is difficult to make a valid statistical comparison because of the small number of resistant cases, this is an important observation that needs to be evaluated by larger studies to examine the interrelationship between in vitro susceptibility and clinical response.

We conclude that a single dose of 1 g of tetracycline is a clinically useful treatment in cholera, especially during an epidemic outbreak, when life-saving treatment is more important than bacteriologic cure. In contrast, a single dose of 400 mg of furazolidone is not useful in the treatment of cholera in adults. However, this drug may be effective in less severe diarrhea such as enterotoxigenic *Escherichia coli* diarrhea and is effective against cholera when given in more prolonged courses.

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