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Effects of Doxycycline in Actively Purging Cholera Patients: a Double-Blind Clinical Trial

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In 51 actively purging cholera patients the efficacy of doxycycline, a long-acting tetracycline, was compared with a placebo and tetracycline hydrochloride. Seventeen patients who were given doxycycline at the recommended dose of 2 mg/kg at the beginning of the study, at 12 h, and at the repeated dose once daily purged a mean volume of 5.1 liters of stool and received an average of 5.7 liters of intravenous fluid. Nineteen patients receiving the placebo purged 10.1 liters of stool and received 9.7 liters of fluid. Fifteen patients given tetracycline hydrochloride at 6-h intervals passed 4.8 liters of stool and received 5.5 liters of fluid. The durations of diarrhea calculated in 8-h periods were 3.5, 8.0, and 4.1 h in the respective groups receiving doxycycline, placebo, and tetracycline. The differences between the doxycycline and placebo treatments and the tetracycline and placebo treatments were statistically significant. Those receiving doxycycline became vibrio-free in about 3 days as compared with 2 days for those receiving tetracycline; the group given the placebo were vibrio positive for the duration of their hospitalization. The results show that in the treatment of cholera the administration of doxycycline once daily has effects equal to those when tetracycline is administered at 6-h intervals. This is a distinct advantage because it decreases the demand on nursing personnel in epidemics. Also, doxycycline may be safely administered in cases of suspected renal failure from prolonged shock in cholera.

The rapid correction of dehydration and the replacement of electrolytes have been primarily responsible for the striking reduction in mortalities in cholera (2, 4, 5). Antibiotics are considered to be very useful adjuncts in cholera therapy because they bring about a significant reduction in the duration of diarrhea and the amount of intravenous (i.v.) fluid required. They also make the patients vibrio-free, which reduces the possibility of transmission. Tetracycline has been found to be the antibiotic of choice, except in small children and pregnant mothers where furazolidone may be substituted (1, 4, 6, 8). These antimicrobial agents, however, must be administered at 6-h intervals, which requires a considerable amount of nursing time.

A temporarily reduced urine output after prolonged dehydration and shock in cholera is not infrequent, particularly in patients who come to a treatment center from remote areas. Acute renal failure may develop in some of these patients. Toxic concentrations of drug in the serum may be produced in these patients if tetracycline hydrochloride is administered. Doxycycline, a tetracycline derivative with a long serum half-life requiring less frequent administration, has been used as a safe antibiotic in renal failure (3, 7).

Since doxycycline seemed to offer some distinct advantages over the short-acting tetracyclines for use in cholera, a therapeutic trial was carried out at the Cholera Research Laboratory during the 1974 to 1975 epidemic, wherein the efficacy of doxycycline was compared with a placebo as well as with tetracycline.

MATERIALS AND METHODS

Patients. Cases admitted with a short history of acute, watery diarrhea and with clinical signs of uncomplicated cholera were initially selected as prospective subjects for inclusion in the study. None were selected if they had been treated outside with antimicrobial agents. After admission, vital signs were recorded and a clinical assessment of dehydration was made. An i.v. infusion with Dacca solution, containing 133 meq of Na^+ per liter, 13 meq of K^+ per liter, 48 meq of HCO_3^- per liter, and 98 meq of Cl^- per liter (4), was used for the correction of dehydration and the replacement of electrolytes. The rate of initial rehydration was varied according to the degree of dehydration and the body weight of the patients. After the initial hydration was completed, which took between 2 and 3 h, the subsequent output of stool, urine, and vomitus, if any, was mea-

sured at 8-h intervals. This volume was matched by the subsequent administration of Dacca solution in the next 8-h interval. Rectal swabs were obtained on admission and cultured for *Vibrio cholerae*, using tellurite-taurocholate agar plates, and for *Shigella* and *Salmonella*, using *Salmonella-Shigella* and MacConkey agar media. Adults purging a volume of stool of 1 liter or more and children between 8 and 15 years passing 500 ml or more in an 8-h period after admission were classified as active purgers and were subjected to the clinical trial. The selection of patients into the placebo, doxycycline, and tetracycline groups was made by picking up cards arranged strictly in that order.

Doses. Doxycycline for oral use in 100-mg capsules and syrups containing 50 mg/teaspoon (5 ml) in coded forms was supplied with identical-looking placebos by the Pfizer Laboratories (Bangladesh) Ltd. The codes were held in a sealed envelope until the completion of the study by the principal investigator. A single, approximate dose of 2 mg of doxycycline per kg was administered at the beginning of the trial followed by another dose at 12 h. Capsules of 100 mg of doxycycline were given to adults above 15 years of age. For children, measured volumes were used according to body weight. The administration was repeated once every 24 h for a total of 4 days, or a course of five doses of capsules or syrup. Tetracycline hydrochloride (Dow Chemical Co., United States) in capsules and syrup was given in doses of 20 mg/kg per 24 h in divided doses at 6-h intervals for a 4-day period. There were no placebos for tetracycline.

Evaluation. Vital signs, the intake of fluid, and the output of stool, urine, and vomitus were recorded every 8 h during the period of diarrhea. Stool and urine were collected in separate containers.

Rectal swabs for culturing *V. cholerae* were taken daily from each patient.

RESULTS

A total of 190 patients were screened for the study; 51 were found to be active purgers and bacteriologically positive for *V. cholerae*. Of these, 19 belonged to the placebo group, 17 belonged to the doxycycline group, and 15 belonged to the tetracycline group. Table 1 shows the mean age, height, and weight of the patients. The mean stool volume passed and the i.v. fluid required before subjecting them to the trial are also shown in Table 1.

Stool volume, i.v. requirements, and duration of diarrhea. The mean volume of total stool passed after the beginning of the administration of antibiotics showed a reduction of 48 and 52% while the patients were treated with doxycycline and tetracycline, respectively, as compared with the placebo. Similarly, there was reduction of 41 and 43% in the requirement of the amount of i.v. fluids. As compared with 64 h as the mean duration of diarrhea while on the placebo, it was only 28 h with doxycycline, or a reduction of 56%, and 33 h with tetracycline, or a reduction of 49%. Table 2 shows the actual values. The differences between the placebo and doxycycline groups and the placebo and tetracycline groups were statistically significant. However, those between the doxycycline and tetracycline groups were not significant.

Duration of *Vibrio* excretion. *V. cholerae* were isolated daily from all patients in the placebo group. They were given tetracycline before discharge. The tetracycline group remained positive for *V. cholerae* for 1.8 ± 0.8 days, whereas the doxycycline group remained positive for 2.6 ± 0.7 days. The difference between the groups was statistically significant ($P < 0.01$).

None of the patients selected for the study developed complications. All patients, including those on the placebo, recovered within a period of 3 to 4 days. No side effects due either to the long-acting or to the short-acting tetracyclines were noted.

DISCUSSION

This study clearly showed that doxycycline, which requires less frequent administration, was as effective clinically as tetracycline, which requires more frequent administration. As much as 6 h of the time of one skilled nurse may be required for the routine administration of a single drug four times in 24 h in a ward with 50 patients. By using doxycycline, this could be reduced to one-third. It may, however, be argued that cholera patients require frequent observation for adjusting the intake of

TABLE 1. *Particulars of cholera patients in the clinical trial*

Group	No. of patients	Age (yr)		Height (cm)		Weight (kg)		Stool volume (liters)[a]		i.v. Given (liters)[a]	
		Mean	SD[b]	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Placebo	19	23	18	147	24	33	13	2.0	1.1	5.2	2.0
Doxycycline	17	18	14	130	25	25	11	2.1	1.7	4.4	2.3
Tetracycline	15	22	16	138	28	30	13	2.0	1.7	4.2	2.2

[a] Before the administration of drugs.
[b] SD, Standard deviation.

TABLE 2. *Effects of the oral administration of placebo, doxycycline, and tetracycline in the treatment of cholera*

Group	Total stool volume (liters)		Total i.v. given (liters)		Duration of diarrhea in 8-h period		*Vibrio* positive (days)	
	Mean	SD[a]	Mean	SD	Mean	SD	Mean	SD
Placebo	10.0	6.0	9.7	4.8	8.0	3.2	All days	
Doxycycline	5.2[b]	4.0	5.7[b]	4.9	3.5[c]	2.1	2.6[b]	0.7
Tetracycline	4.8[b]	3.1	5.5[b]	3.9	4.1[c]	2.1	1.8[b]	0.8

[a] SD, Standard deviation.
[b] $P < 0.01$.
[c] $P < 0.001$.

fluid according to the rate of purging and that the administration of a drug would require a nurse to keep a more watchful eye over the patients.

The price of doxycycline per dose is considerably higher than that for ordinary tetracycline; however, the total cost for a course of therapy in cholera makes it only slightly more expensive than with ordinary tetracycline. The price of 5 gm of a local brand of tetracycline is $1.40, which may be compared with $1.75 for 600 mg of doxycycline. However, the cost of the antibiotic is only a fraction of the total cost in the management of cholera, where personnel and i.v. fluids are the more expensive items.

With the advent of modern replacement therapy, using balanced fluids in adequate quantities, acute renal shutdown after prolonged shock in cholera has become rather infrequent (9). Caution, however, has to be observed when a patient from a rural area arrives in a hospital after an interval of a number of days from the onset of acute diarrhea. These patients coming from rural areas are often treated at their home with an inadequate quantity of fluid. They may develop a prolonged, but frequently temporary, suppression of urine, correctable by adequate rehydration. As a precautionary measure, ordinary tetracycline is withheld from these patients until they have started to pass urine in adequate quantities. Doxycycline may be used to reduce the duration of diarrhea in these patients because this antibiotic has been found to be safe for use in renal failure (3, 7).

The marginal advantage of tetracycline over doxycycline in making a patient vibrio-free at an earlier time is probably due to its continued high concentration in the gut by frequent administration. Doxycycline, on the other hand, is quickly absorbed and slowly excreted (10). Cholera is known to shorten the mean transit time through the small intestine to as little as 40 min in some patients. This short transit time may not allow adequate time for the complete absorption of doxycycline. It is, however, reassuring to note that in spite of a known, short mean transit time in cholera and less frequent administration, the clinical effect of doxycycline was similar to that of tetracycline.

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