Clinical trials

Single dose tetracycline in cholera

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SUMMARY A randomised clinical trial was carried out to explore the efficacy of single dose tetracycline therapy in cholera. One hundred and eighteen adult patients were assigned to receive either tetracycline in a single 1 g, or a single 2 g dose, or tetracycline 500 mg every six hours four times, or no antibiotics as controls. The means of total liquid stool volumes after treatment were lower in the single 1 g dose group (168.0 ± 20.9 ml/kg), in single 2 g dose group (229.5 ± 45.6 ml/kg), and multiple dose group (214 ± 28.5 ml/kg), than in the control group (499.1 ± 56.5 ml/kg) ($p < 0.05$). Similarly, the means of durations of diarrhoea and intravenous fluid requirements were significantly lower in the single dose and multiple dose tetracycline groups, than in the controls ($p < 0.05$). The mean durations of excretion of *Vibrio cholerae* were significantly shortened from 3.9 ± 0.2 days in the control group to 1.9 ± 0.2 days in single 1 g dose, to 2.2 ± 0.4 days in single 2 g dose and 1.3 ± 0.1 days in multiple dose groups, respectively ($p < 0.05$). Three patients in the single 1 g dose group and two patients in single 2 g dose group had clinical relapses with excretion of *V. cholerae* during the relapses, but this was not significantly more frequent than that in the multiple dose group ($p > 0.05$). These findings suggest that although multiple dose tetracycline therapy remains the best choice, a single dose of either 1 g or 2 g tetracycline appears to be a reasonable alternative for the treatment of cholera as an adjunct to rehydration therapy.

Cholera is the severest of all forms of watery diarrhoeal diseases that may lead to dehydration and death. The effectiveness of tetracycline as an adjunct to rehydration therapy in the clinical management of acute cholera has been well documented.^{1,2} Tetracycline significantly shortens the period of diarrhoeal illness and reduces the volume of stool output and fluid requirements of patients with severe cholera.¹⁻³ Treatment with tetracycline given for varying lengths of time (1, 2, 3, or 4 days) made no differences in clinical response.^{1,2} Also increasing the dose of tetracycline from two to three times did not appear to enhance its therapeutic effect.² The most effective dose and duration of tetracycline therapy in cholera still remains unresolved.³ The advantages of single dose therapy include a saving of treatment cost, improved patients compliance and ease of administration, particularly when there is an epidemic.

Single dose doxycycline (200 mg) although more expensive was found to be as effective as multiple

dose therapy in cholera.⁴ The objective of our study was to evaluate in a controlled trial, the clinical and bacteriological efficacy of three different treatment regimens, (a) a single dose of 1 g or (b) 2 g tetracycline and (c) a multiple dose of 2 g tetracycline in adult patients with severe cholera.

Methods

PATIENTS

The study was carried out at the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh. Adult patients who visited the hospital with a clinical history of acute watery diarrhoea of less than 24 hours duration with vibrios in faeces identified by dark field microscopy,⁵ evidence of dehydration according to WHO clinical criteria,⁶ and no antibiotic use within seven days before admission were selected for the study. The diagnosis of cholera was confirmed by bacteriologic identification of *V. cholerae*. Written informed consent was obtained. Patients were weighed and put on cholera cots designed to facilitate accurate separation of stool and urine. After a brief initial clinical assessment of the

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patient, intravenous rehydration was started using an isotonic solution containing 133 mmol sodium, 13 mmol potassium, 98 mmol chloride and 48 mmol acetate per litre. Intravenous therapy was continued until diarrhoea stopped. Progress of hydration was assessed clinically by general appearance of the patient, good radial pulse, normal blood pressure, normal skin turgor, gain in body weight and good urination. Food was allowed as soon as the patients were able to eat.

Treatment was randomised among single 1 g dose, single 2 g dose, multiple dose or no tetracycline. Randomisation was done for each patient by drawing a slip labelled SD1, SD2, MD or O from an envelope initially filled with 50 SD1, 25 SD2, 25 MD, and 25 O's. Multiple dose therapy patients received 500 mg tetracycline six hourly for four doses. Tetracycline was given orally.

Intravenous fluid intake and stool, vomitus and urine output were carefully measured every eight hours until diarrhoea stopped. 'End of diarrhoea' was defined to have occurred at the end of the last eight hour period in which liquid stool was passed. If a patient passed soft or formed stool thereby reaching 'end of diarrhoea' and subsequently passed liquid stool, this was considered to be a clinical relapse.

Catheter specimens of stool or rectal swabs were obtained daily for culture of *V cholerae* until cultures became negative for three consecutive days. Bacteria from colonies typical of *V cholerae* were tested for agglutination with polyvalent O group 1 specific antisera and were tested for haemagglutinating activity with chicken erythrocytes.

If a patient become bacteriologically negative for at least two consecutive days and was subsequently positive for *V cholerae*, this was considered to be bacteriological relapse.

After the end of the study, data of the four groups of patients were analysed by two tailed normal test (Z test), χ^2 and Fisher exact test.

Results

The 118 patients were comparable in mean age, sex

distribution, clinical dehydration, body weight and duration of diarrhoea before admission (Table 1). The majority of patients in each group were infected with Ogawa serotype, classical biotype, of *V cholerae*. All 118 isolates of *V cholerae* were susceptible to tetracycline by *in vitro* testing.

Patients treated with single and multiple doses of tetracycline responded quickly with sharp reductions in stool outputs in nearly all patients by the second eight hour period after treatment. Measurements of stool volumes at 16 hourly intervals after treatment showed that all three groups receiving tetracycline produced significantly less stool than the controls at 32, 48, 64, and 80 hour after treatment ($p<0.05$, Figure). The mean duration of diarrhoea of 35.2 h after single 1 g dose, 42.8 h after single 2 g dose and 37.4 h after multiple dose treatment were significantly less than the mean of 85.4 h for the controls ($p<0.05$) (Table 2). Similarly, the means of total stool output and intravenous fluid requirements in

Figure Effect of therapy on stool output in cholera patients. Points are mean value of stool output during 16 h periods and brackets are 1 SEM unit. Mean values at times of 32, 48, 64, and 80 hour after treatment were significantly lower in patients treated with both single and multiple doses of tetracycline when compared with controls (<0.05).

Table 1 Comparison of the characteristics of cholera patients on admission treated with single 1 g or 2 g dose tetracycline, multiple dose tetracycline and controls without tetracycline. Values are means $\pm$ SEM or percentages of patients with the features

Characteristics	Single 1 g dose (n=45)	Single 2 g dose (n=23)	Multiple dose (n=25)	Controls (n=25)
Age in years	30.4 $\pm$ 2.1	28.4 $\pm$ 2.5	26.3 $\pm$ 1.9	33.2 $\pm$ 3.2
Male/female	30/15	12/11	10/15	11/14
Body weight in kg after rehydration	42.9 $\pm$ 1.1	43.6 $\pm$ 2.0	40.7 $\pm$ 1.4	42.5 $\pm$ 1.1
Duration of diarrhoea before admission (h)	13.3 $\pm$ 1.1	12.1 $\pm$ 1.1	13.8 $\pm$ 1.2	16.4 $\pm$ 1.4
Clinical dehydration:				
Moderate	22%	20%	12%	12%
Severe	78%	80%	88%	88%

the single doses and multiple dose tetracycline groups were less than half of that of the controls. The mean durations of vibrio excretion in stool were 1.9 days in single 1 g dose, 2.2 days in single 2 g dose, 1.3 days in multiple dose but 3.9 days in control group ($p < 0.05$). Increasing the single dose of tetracycline from 1 g to 2 g did not enhance its therapeutic efficacy (Table 2).

Clinical relapses were defined as the return of liquid stool after passing solid stool. Three patients in the single 1 g dose treatment group, two patients in the single 2 g dose group experienced clinical relapses and all had positive stool cultures for *V. cholerae* of the same biotype and serotype as they had in their initial episodes. These relapses occurred two to three days after the patients had ceased passing liquid stool and four of these patients required intravenous fluid therapy. No clinical relapses occurred in patients in the multiple dose and control groups. The incidences of clinical relapses in the single 1 g dose group of 3/45 and 2/23 in the single 2 g dose group, however, were not significantly greater than in the multiple dose group (Fisher's Exact Test).

The bacteriological responses were prompt in all single and multiple dose groups (Table 3). By day 2, or just 24 h after the start of treatment, the rates of isolating *V. cholerae* from stool cultures were significantly less in three treatment groups than in the

control group ($p < 0.05$). At this time, the rate of 2/25 isolations in the multiple dose groups was significantly less than 13/45 in the single 1 g dose group ($p < 0.05$), and than 10/23 in the single 2 g dose group ($p < 0.05$). Thereafter, the rates of isolation were similarly low in both treatment groups. Bacteriological relapses were defined as the isolation of *V. cholerae* from a patient who had negative cultures on two preceding days. There were seven bacteriological relapses in the single 1 g dose group, two relapses in the single 2 g dose group, and three relapses in the multiple dose group.

Discussion

Although emergence of multiply antibiotic resistant *V. cholerae* has been reported in few cases in Bangladesh* and Tanzania,⁹ tetracycline has remained the drug of choice in the treatment of cholera and it had been proved beyond doubt that it reduces gastrointestinal fluid loss, duration of diarrhoea and also eliminates *V. cholerae* from stool within 48 hours. Using single dose antibiotic therapy the physician can ensure that the patient has taken his full course of therapy and does not have to depend on patient compliance. The efficacy of single large dose therapy in infections is probably related to the rapid attainment of high concentration of the drug at the

Table 2 Duration of diarrhoea, output of stool, intravenous fluid requirement, and vibrio excretion of cholera patients treated with single dose tetracycline 1 g or 2 g, multiple dose tetracycline 500 mg every six h four times, and controls not receiving antibiotic. Values are mean $\pm$ SEM*

	Duration of diarrhoea after treatment (h)	Total liquid stool output in ml/kg during hospital stay	Intravenous fluid requirement (ml/kg)	Duration of positive vibrio culture in stool (day)
Single 1 g dose tetracycline (n=45)	35.2 $\pm$ 2.8	168.0 $\pm$ 20.9	202.9 $\pm$ 23.6	1.9 $\pm$ 0.2
Single 2 g dose tetracycline (n=23)	42.8 $\pm$ 6.7	229.5 $\pm$ 45.6	260.7 $\pm$ 48.9	2.2 $\pm$ 0.4
Multiple dose tetracycline (n=25)	37.4 $\pm$ 3.4	214.5 $\pm$ 28.5	258.3 $\pm$ 29.3	1.3 $\pm$ 0.4
Control (n=25)	85.4 $\pm$ 5.6	499.1 $\pm$ 56.5	526.8 $\pm$ 63.8	3.9 $\pm$ 0.2

*Means of duration of diarrhoea, total liquid stool output, intravenous fluid requirement, and duration of vibrio excretion for both single dose and multiple dose tetracycline were significantly lower than for controls ($p > 0.001$ by normal 'Z' test). Means of these determinations were not significantly different among single doses and multiple dose groups ($p > 0.05$).

Table 3 Isolation of *V. cholerae* from stools of patients treated with single dose tetracycline, multiple dose tetracycline and controls without tetracycline. Numbers are cases with positive culture on each day in hospital. R refers to number of bacteriological relapses, defined as 2 or more days of negative culture followed by a positive culture

Treatment group	Day 1	Day 2*	Day 3†	Day 4†	Day 5†	Day 6†	Day 7
Single 1 g dose	45	13	7	5+5 R	3+2 R	2	1
Single 2 g dose	23	10	3	4+2 R	3	2	1
Multiple dose	25	2	0	0+3 R	1	1	0
Control	25	19	18	14+1 R	14+2 R	14+1 R	0

*On day 2, the frequency of positive cultures was significantly greater in controls than in cases treated with either single or multiple doses of tetracycline ($p < 0.05$ by χ^2 test). The frequency of positive culture was significantly greater in cases treated with single doses than with multiple doses ($p < 0.05$ by χ^2 test); †On days 3–6, the frequencies of positive cultures were greater in controls than in patients treated with either single or multiple doses of tetracycline.

site of infections causing rapid destruction of the invading organisms.

Our study has shown that single 1 g or 2 g dose tetracycline was as effective as multiple dose therapy when mean values of duration of diarrhoea, liquid stool output, intravenous fluid requirement, and excretion of *V. cholerae* were compared. Although initial response is good, clinical relapses with excretion of *V. cholerae* during the relapses occurred in three patients (6.6%) in the single 1 g dose group and two patients (8.7%) in the single 2 g dose group while no relapse occurred in the multiple dose group. This frequency of clinical relapse in the patients treated with single dose tetracycline was not statistically significant. Larger studies will be required to determine whether the single dose is as effective as the multiple dose when treating relapses.

The duration of excretion of *Vibrio cholerae* after single dose tetracycline therapy, however, is not as effectively shortened as with multiple dose tetracycline therapy. It is not yet clear whether these asymptomatic culture positive patients represent a significant public health risk to the community, as symptomatic cholera patients only represent a small fraction of the total number of people infected with and excreting *Vibrio cholerae* during an epidemic.

In a previous study it was shown that in clinical cholera, the duration of antibiotic therapy appeared to be more important than the amount given.² In this study, we have also observed that merely increasing in the dose of tetracycline does not enhance its therapeutic efficacies.

The primary and life saving treatment for clinical cholera remains rehydration and maintenance of continuing losses by oral rehydration or intravenous fluid. Treatment of adult patients with single dose 1 g or 2 g tetracycline in addition to careful attention to rehydration should give satisfactory results especially where supervision of patients is minimal such as outpatient clinics and rehydration centres and when busy physicians can ensure that the patient has taken his full course of therapy and does not have to rely on patients compliance. Another advantage of single 1 g dose therapy is that only half the amount of tetracycline (1 g) is used compared with multiple dose therapy. Clinical relapses were observed, however, in 7% cases with single dose therapy. Therefore

multiple dose therapy is preferable but single dose treatment might be used in emergencies or when patients with relapses have access to care.

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