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SECTION I - RESEARCH PROTOCOL

1) Title: Single Dose Doxycycline for Cholera

2) Principal Investigator: David A. Sack, M.D.

3) Starting Date: March, 1977

4) Completion Date: October, 1977

5) Total Direct Cost: $ 11,066

6) Abstract Summary:

Sixty patients will be studied in a randomized, unblinded, antibiotic trial for the treatment of cholera comparing single dose doxycycline (4 mg/kg) with multiple dose doxycycline (2 mg/kg/dose, daily for 4 days). Multiple dose doxycycline has previously been found equal in effectiveness with tetracycline. Patients will be compared with respect to duration of diarrhea, duration of positive stool culture for vibrio, volume of I.V. fluid used and volume of diarrheal stool. If effective, single dose doxycycline would further simplify and lower the cost of the treatment of cholera.

7) Reviews:

a) Research Involving Human Subjects: _____

b) Research Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller, Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective: The long-term goal of this project is to simplify the treatment of cholera, lower the cost of treating cholera, and thereby make maximally effective cholera treatment available to persons living in rural and medically under-developed areas.

2. Background: The treatment of cholera has undergone several advances in recent years which have both simplified therapy and decreased mortality from the disease. These include a standardized intravenous solution for reversing shock, an oral fluid for maintaining hydration and antibiotics to shorter the duration of symptoms. Of the antibiotics, tetracycline is the drug of choice. Doxycycline, however, has been shown to be equally effective in shortening the diarrhea when given for 4-days.

Several characteristics distinguish doxycycline from other tetracyclines and make this drug useful in the treatment of enteric infections: 1) A prolonged half life (16-20 hours) make possible a single daily dose. 2) Toxic levels of drug are not retained in renal failure with the usual oral dosages. 3) Although the drug is excreted via both kidney and liver, a primary route of excretion is directly through the mucosa of the small intestine.

This mode of excretion places the drug directly at the site of infection. 4) Much of the drug is inactivated before reaching the large bowel; hence, there is less selection for resistant fecal flora. These characteristics would seem to make doxycycline an excellent antibiotic for the treatment of tetracycline sensitive enteric infections - especially cholera. If equally effective with tetracycline, the single dose therapy would further simplify the treatment of cholera, especially for outpatients since this would eliminate problems of patient compliance. It would also simplify the treatment of inpatients since no further antibiotics would need to be given after initial therapy.

Workers in Calcutta have compared doxycycline in three dosages schedules to the standard tetracycline treatment of cholera. They interpret their data as showing that 300 mg doxycycline, single dose, is equally effective with tetracycline, while 200 mg single dose or 200 mg followed by 100 mg (two doses) is less effective. The clinical differences between the groups were small, however, and it appeared that all patients in all groups were successfully treated since the longest duration of purging was 30 hours following admission. While 300 mg may be slightly more effective that 200 mg. oral doxycycline is associated with nausea and vomiting, and this is a dose related effect. 200 mg is the usual

adult dose for most infections in which doxycycline is used and would seem more appropriate.

In our study to date, comparing 200 mg doxycycline single dose, with multiple dose doxycycline, we have included 29 persons in the study; 16 have been treated with single dose and 13 with multiple dose. There are no differences in the mean duration of diarrhea, duration of positive stool cultures, or total diarrheal stool output.

It is understood that no antibiotic replaces the need for a adequate hydration therapy, and it is likely that if successful, single dose doxycycline would be combined with oral fluid therapy in a minimal care setting for the treatment of cholera in a later protocol.

3. Rationale: We plan to test the efficacy of single dose doxycycline in the treatment of cholera by comparing single dose (200 mg) with multiple dose doxycycline (which has previously been shown equal to tetracycline). If successful single dose therapy would further simplify the treatment of cholera.

B. SPECIFIC AIMS

To determine the efficacy of single dose doxycycline, 200 mg, taken immediately after rehydration, in the treatment of cholera.

C. METHODS OF PROCEDURE

Sixty patients admitted to the Cholera Research Hospital will be studied who meet the following criteria:

1. Cholera syndrome with moderate to severe dehydration.
2. Male ≥ 5 years of age.
3. Continued purging during a 4-hour observation period.
4. Stool exam positive for V.cholerae by darkfield exam.
5. Signed informed consent of patient (or parent in case of children).

Patients who meet these criteria will be studied in the research ward of the hospital.

The following will be performed on admission:

1. History and physical.
2. Urinalysis.
3. Stool exam for ova, parasites, fecal leukocytes, darkfield and culture.
4. Blood for complete blood count, electrolytes, specific gravity, creatinine, blood urea nitrogen.

Patients will be rehydrated using standard I.V. solution; hydration will be maintained with I.V. solution for the duration of purging. Food and water will be allowed ad lib.

Each patient will be randomized to one of two oral antibiotic dosage schedules (see randomization sheet):

1. Single dose doxycycline:
   - ≥15 years - 200 mg given immediately after hydration
   - <15 years - 4 mg/kg given immediately after hydration
2. Multiple dose doxycycline:
   - ≥15 years - 100 mg given immediately after hydration then 100 mg daily for 3 days.
   - <15 years - 2 mg/kg given immediately, then 2 mg/kg in 12 hours, then 2 mg/kg daily for 3 days.

Evaluation of patients will be as follows:

1. Vital sings, Q8H
2. Intake of fluids (I.V. and p.o.) Q8H
3. Output of stool, urine, vomitus, Q8H
4. Stool culture daily.

Patients will remain in the hospital for 4-5 days and in all cases will have two days of culture negative stools for Vibrio. Patients with a stool culture positive for Vibrio on day 5 will be judged a

bacteriological failure, and will be treated with tetracycline in standard doses for cholera.

Randomization of patients to one of the two treatment schedules will be by a predetermined table taken from a list of random numbers. Evaluations of patients will not be blinded.

Sixty patients will be needed for this study. This is based on a assumption that the multiple dose group will have a 95% clinical success rate, (Success is defined as the cessation of purging within 3 days) and we would consider it clinically significant if the success rate for single dose was less that 85%. The Fisher exact test (for success or failure of treatment) and T Test (for mean I.V. fluids used and stool output) will be used as statistical tests.

D. SIGNIFICANCE

If successful, single dose doxycycline for cholera would further simplify treatment and lower the cost of treatment. These two factors are of major inportance in the delivery of medical care to people in developing countries, especially in rural areas.

E. FACILITIES REQUIRED

1. Office Space: For principal investigator and study physicians on the ward. No additional space needed.

2. Laboratory Space: Only the routine laboratories will be needed.

3. Hospital Resources: Beds - 60 patients X 5 days/patient. 300 patient days over a period of 6 months.

4. Animal Resources: None

5. Logistical Support: None

6. Equipment: None

7. Other: None

F. COLLABORATIVE ARRANGEMENTS

None

TREATMENT SCHEDULE FOR SINGLE DOSE DOXYCYCLINE FOR CHOLERA

Patient Study	Drug Schedule	Patient Study	Drug Schedule	Patient Study	Drug Schedule	Patient Study	Drug Schedule
1	S *	21	M	41	M	61	M
2	M **	22	S	42	S	62	M
3	S	23	S	43	M	63	S
4	M	24	M	44	M	64	M
5	S	25	M	45	S	65	M
6	S	26	S	46	M	66	S
7	M	27	S	47	S	67	S
8	S	28	M	48	S	68	S
9	S	29	S	49	S	69	M
10	S	30	M	50	M	70	M
11	M	31	S	51	M	71	S
12	M	32	M	52	S	72	M
13	M	33	M	53	S	73	S
14	S	34	S	54	M	74	M
15	S	35	M	55	M	75	M
16	M	36	M	56	S	76	S
17	M	37	S	57	S	77	S
18	S	38	M	58	M	78	M
19	S	39	S	59	S	79	S
20	S	40	M	60	M	80	S

* Single Dose Doxycycline

** Multiple Dose Doxycycline.

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DE, S., Chaudhuri, A., Dutta, P., Dutta, D., DE, S.P. and Pal, S.C. Doxycycline in the treatment of cholera. Bull. World Health Organ., 54, 177-179, 1976.

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GREENOUGH, W.B. III, Rosenberg, I.S., Gordon R.S., et al. Tetracycline in the treatment of cholera. Lancet 1: 355-357, 1964.

RAHAMAN, M.M., Majid, M.A., Alam, A.K.M.J. et al. Effects of Doxycycline in Actively Purging Cholera Patients: A Double-Blind Clinical Trial. Antimicrob Agents Chemotherapy. 10: 610-612, 1976.

WALLACE, C.K., Carpenter, C.C.J., Mitra, P.P. et al. Oral Tetracycline Therapy in Cholera. Trans. Roy. Soc. Trop. Med. Hyg. 59: 621-627, 1965.

WALLACE, C.K., Anderson, P.N., Brown, T.C., Khanra, S.R., Lewis, G.W., Pierce, N.F., Sanyal, S.N., Segre, G.V. and Waldman, R.H. Optimal Antibiotic Therapy in Cholera. Bull. Wld. Hlth. Org. 39, 239-245, 1968.

SECTION III - BUDGET

A. DETAILED BUDGET

1. PERSONNEL SERVICES

Name	Position	% of time	Annual Salary	Project Requirements TAKA	DOLLARS
Dr. David Sack	Investigator	15%	$34,750	-	5,213
Dr. Shiraz	Co-investigator	15%	Tk.36,384	5,458	-
Dr. Rabbani	Co-investigator	15%	Tk.27,084	4,063	-
Dr. Asma	Co-investigator	15%	Tk.27,084	4,063	-
Secretary		15%	Tk.27,084	4,063	-
			Sub Total:	17,647	5,213

2. SUPPLIES AND MATERIALS

Items	Unit Cost	Amount Required		
Paper, pens, Misc.			3,000	-
		Sub Total:	3,000	-

3. EQUIPMENT

Items	Unit Cost	Amount Required	-	-

4. PATIENT HOSPITALIZATION

			—	—
400 patient days @ Tk. 135/- day			54,000	-
Routine tests - Biochemistry			360	-
Bacteriology			5,425	-
Clinical Pathology			1,120	-
		Sub Total	60,905	-

	Project Requirements: TAKA	DOLLARS
5. OUTPATIENT CARE	-	-
6. CRL TRANSPORT	-	-
7. TRAVEL AND TRANSPORTATION OF PERSONS	-	-
8. TRANSPORTATION OF THINGS	-	-
9. RENT, COMMUNICATION & UTILITIES	-	50
10. PRINTING AND REPRODUCTION		
Local xerox, stencil	1,000	-
Publication costs		300
Sub Total:	1,000	300
11. OTHER CONTRACTUAL SERVICES	-	-
12. CONSTRUCTION, RENOVATION, ALTERATIONS	-	-

B. BUDGET SUMMARY

	Category	Year 1 Taka	Year 1 Dollars	Year 2 Taka	Year 2 Dollars	Year 3 Taka	Year 3 Dollars
1.	Personnel	17,647	5,213	NONE		NONE	
2.	Supplies	3,000	-				
3.	Equipment	-	-				
4.	Hospitalization	60,905	-				
5.	Outpatients	-	-				
6.	CRL Transport	-	-				
7.	Travel Persons	-	-				
8.	Transportation Things	-	-				
9.	Rent/Communication	-	-50				
10.	Printing/Reproduction	1,000	300				
11.	Contractual Service	-	-				
12.	Construction	-	-				
	Total:	82,552	5,563				

Total $ - 11,066

Conversion rate $ 1.00 = Tk. 15.00

ABSTRACT SUMMARY - SINGLE DOSE DOXYCYCLINE FOR CHOLERA

Two dosage schedules of doxycycline, a long acting tetracycline, will be evaluated in the treatment of cholera. Actively purging male patients, over 5 years, with a dark field examination of stool positive for V. cholerae will be admitted to the study. These patients will be assigned to either a single dose of doxycycline (200 mg) or multiple doses of doxycycline (100 mg/dose). All patients will be treated with appropriate rehydration. The two groups will be compared with regard to duration of diarrhea, volume of diarrhea, and number of days with a -ositive culture for Vibrio. If single dose doxycycline is effective in shortening diarrhea from cholera, this dosage would be useful in further simplifying the treatment of cholera.

1. Children 5 years of age are included in this study because cholera, to a great extent, is a disease of children. The efficacy of this treatment must be determined in the group at risk which includes children.

2. All patients with cholera are at risk of complications secondary to dehydration and shock. All patients will be treated with appropriate fluid therapy. Since antibiotics are not essential in the treatment of cholera, no added risk is involved in comparing two dosage schedules of an antibiotic. Although tetracycline in higher doses for a longer duration may cause dental staining in children, it is

not seen in the dosage used in this study.

3. There are no increased potential risks from the study itself. All patients will be treated optimally for their cholera with appropriate fluid and electrolyte therapy.

4. Patients will be identified by study number. All records will be kept in a locked office.

5. Signed consent will be obtained from each subject, or if he is a minor, from the parent.

6. N.A.

7. All patients will be treated for their cholera. If the single dose doxycycline is equally effective with multiple dose in shortening the diarrhea of cholera, this would further simplify and lower the cost of treating cholera.

8. Blood and stool specimens will be obtained.

PERMISSION FORM - SINGLE DOSE DOXYCYCLINE FOR CHOLERA

The Cholera Research Hospital is carrying out research to determine the best treatment for cholera. We would like you to participate in a study under the direction of Dr. David Sack to determine whether one dose of doxycycline, an effective antibiotic for cholera, is as good as the same drug given for four days. If this new dosage schedule is successful it would greatly simplify the treatment of cholera especially for people living in rural areas in Bangladesh. If you agree to participate in this study you can expect the following:

1. We will treat your cholera. You will be in the hospital for about four days recovering from your illness.

2. You will receive doxycycline, an antibiotic for cholera, in one of two ways. Either a single dose on the first day or many smaller doses for four days.

3. There is no risk to your health - no special tests will be done.

4. Your medical records will be kept confidential.

5. You do not have to participate in the study. If you do enter the study you are free to leave the study at any time. If you decide not to enter the study or if you leave the study, you may still be treated here at the Cholera Hospital for your illness. Your decision regarding the study will not jeopardise your medical care.

6. We will answer any questions you have.

If you agree to participate in this study, please sign your name here.

_____

_____ Date

If you agree to allow your child to participate in the study described above, please sign your name here.

_____

_____ Date

PROCEDURES FOR MAINTAINING CONFIDENTIALITY

Patients admitted to the study will be given a study number; records will be kept according to study number and all data will be kept in a locked file in the investigator's locked office. Following completion of the study, all identifying information will be cut off from the data sheet and the clinical information only will be kept at the Cholera Research Laboratory in a locked data storage office. Results of the study will be published in a medical journal and no identifying information will be included in the report of this study.