chment 1.
E SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date 07 July 1991
10 July 1991

cipal Investigator Dr [illegible].N. Alam
ication No. 91-007
e of Study "Randomized double-blind
al of single-dose doxycycline in the
atment of cholera in children"

Trainee Investigator (if any) _____
Supporting Agency (if Non-ICDDR,B) _____
Project status:
(✓) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

le the appropriate answer to each of the following (If Not Applicable write NA).

Source of Population:
(a) Ill subjects (Yes) No
(b) Non-ill subjects Yes (No)
(c) Minors or persons under guardianship (Yes) No

Does the study involve:
(a) Physical risks to the subjects Yes (No)
(b) Social Risks Yes (No)
(c) Psychological risks to subjects Yes (No)
(d) Discomfort to subjects (Yes) No
(e) Invasion of privacy Yes (No)
(f) Disclosure of information damaging to subject or others Yes (No)

Does the study involve:
(a) Use of records, (hospital, medical, death, birth or other) (Yes) No
(b) Use of fetal tissue or abortus Yes (No)
(c) Use of organs or body fluids (Yes) No

Are subjects clearly informed about:
(a) Nature and purposes of study (Yes) No
(b) Procedures to be followed including alternatives used (Yes) No
(c) Physical risks (Yes) No
(d) Sensitive questions (Yes) No
(e) Benefits to be derived (Yes) No
(f) Right to refuse to participate or to withdraw from study (Yes) No
(g) Confidential handling of data (Yes) No
(h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure (Yes) No

5. Will signed consent form be required:
(a) From subjects Yes No
(b) From parent or guardian (if subjects are minors) (Yes) No
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Committee:
✓ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
✓ Protocol (Required)
✓ Abstract Summary (Required)
✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
✓ Informed consent form for subjects
___ Informed consent form for parent or guardian
___ Procedure for maintaining confidentiality
___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

gree to obtain approval of the Ethical Review Committee for any changes
lving the rights and welfare of subjects before making such change.

Principal Investigator

Trainee

91-007.
10.7.91

SECTION I - RESEARCH PROTOCOL

1. Title	:	Randomized double-blind trial of single-dose doxycycline in the treatment of cholera in children.
2. Principal Investigator	:	Dr A.N. Alam
Co-Investigators	:	Dr M.R. Islam Medical Officer (to be named)
Consultant	:	Dr D. Mahalanabis
3. Starting date	:	As soon as approval is granted
4. Completion date	:	Two years after approval is granted
5. Total direct cost	:	US$ 59270.00
Funding Source	:	WHO
6. Scientific Programme	:	This protocol has been approved by the Clinical Sciences Division

Associate Driector, CSD ---------- Mahalanabis

Date: ---------- 8/7/91 ----------

7. Abstract summary

A randomized double blind prospective controlled study will be carried out on 180 patients aged 3 to 12 years with proven cholera to compare the relative efficacy of single dose doxycycline with tetracycline in the treatment of cholera. Patients will be divided into two equal groups of fifty patients each who will receive either a single dose of 5 mg/kg body weight of doxycycline orally given on the first day of hospitalization or multiple doses of tetracycline (50 mg/kg/day 6 hourly for 3 days). All patients will receive I.V. rehydration therapy followed by oral maintenance fluid. Success of therapy will be determined by comparing the purging and rehydration volumes at 8 hourly intervals, and by comparing the excretion of *V. cholerae* in the stool. If a single dose of doxycycline, is as effective as multiple doses of tetracycline, this regimen will help eliminate problems of patients compliance and simplify logistics in treating cholera patients, especially in field situations or during epidemics.

8. Reviews:

a. Chairman, Ethical Review Committee : ----------

b. Chairman, Research Review Committee: ----------

c. Director, ICDDR,B : ----------

SECTION II - RESEARCH PLAN

A. Objectives

This study aims at evaluating the efficacy of a single-dose doxycycline as an alternative to standard multiple doses of tetracycline in the treatment of children with cholera.

B. Background

Patients with cholera having varying degrees of clinical severity can be effectively treated by using intravenous (I.V.) fluid alone. Simultaneous administration of antibiotic therapy helps in decreasing the volume of stool, duration of diarrhoea and the excretion of vibrios in the stool. This decreases the need for I.V. fluid and nursing care which may be in critical supply during outbreaks in rural communities. Tetracycline in different doses has been found to be consistently effective in the treatment of cholera due to tetracycline sensitive strains (1,2). Tetracycline was used in treatment of cholera in children (3,4,5) where it was found to be the most effective of antibiotics tested in reducing stool volume, I.V. fluid requirement, the duration of diarrhoea and positive stool culture. Of 11% of patients attending the Clinical Research Centre (CRC) of ICDDR,B suffering from cholera, 80% of *V.cholerae* isolated showed resistance to furazolidone and about 50% resistance to ampicillin (ICDDR,B CRC surveillance system). In a situation like cholera where the clinical onset and progress could be dramatic with increased risk of mortality if

intervention is delayed, use of tetracycline for the treatment of acute and severe cholera would, in our opinion, outweigh the possibility of staining of teeth following a short-term use. Doxycycline, a long-acting tetracycline, has also been shown to be effective clinically when given as a single dose of 200 mg or 300 mg (5,6) or over a period of four days (7). Multiple doses of tetracycline has been found to be superior to single-dose tetracycline or doxycycline in shortening the duration of vibrio excretion in stool (6,8). In outpatient clinics or even in hospitals in patients, effective single-dose therapy would save nursing time and would reduce hospitalization cost due to a more rapid turnover of patients. In field situations during an epidemic, multiple dose therapy may not be possible because of lack of supervised administration of antibiotics.

Doxycycline appears to be an excellent antibiotic for cholera (except in those unusual situations with tetracycline resistant *V. cholerae*). Its intestinal absorption is not impaired by the presence of food, and nearly 100% of a dose is absorbed. With a half life of 15-20 hours, therapeutic plasma level persists much longer than with tetracycline. For usual infections where tetracycline is normally used Q.I.D., doxycycline can be given once daily. Doxycycline is excreted through the kidneys and liver (enterohepatic circulation) but it is also excreted directly across the small intestinal mucosa, placing the antibiotic at the location where it can be most

effective. Because of the multiple excretion mechanisms, toxic levels do not usually accumulate, even in patients with renal or hepatic failure.

One disadvantage of doxycycline is its association with nausea and vomiting if given orally. This side effect is dose related (being more common with 300 mg than 200 mg given in adults) and can be lessened by giving the drug with or after food. Duration of treatment with tetracycline in cholera is very short, usually 3 days, and even two days of therapy can be effective. This is quite different from other infections where a minimum course of seven days of antimicrobial therapy is desirable. Scientific literature indicate that the use of tetracycline in a short course during the first six years of life, specially if such treatment is given for the first time to a patient, is usually associated with negligible pigmentation of teeth (9). Doxycycline, a semi-synthetic derivative of oxytetracycline, binds less to calcium than other tetracyclines do. It is for this reason that doxycycline is expected to cause even less tooth staining (10).

Recently, the World Health Organization has been revising its recommendations regarding the use of doxycycline in cholera with special reference to situations in which single dose treatment would be especially appropriate. These situations include rural treatment centres, refugee camps, and other field settings where treatment supervision is minimal. A recent study

conducted at ICDDR,B has clearly demonstrated the efficacy of single dose (300 mg) doxycycline while compared with standard multiple doses of tetracycline (11). The duration of diarrhoea, vomiting, stool output during first 24 hours or total stool output and total ORS consumption till cessation of diarrhoea were similar between the groups receiving conventional tetracycline and high single-dose (300 mg) doxycycline. The proportion of patients who had vomiting was higher in doxycycline groups combined compared to the tetracycline group, although almost equal numbers of patients in each group required unscheduled intravenous therapy during antibiotic treatment.

C. Specific objective

To compare the efficacy of single dose doxycycline therapy with the efficacy of multiple dose tetracycline therapy on the clinical course of cholera in children aged three to twelve years.

D. Rationale

In the treatment of cholera, the use of an effective antimicrobial agent, such as tetracycline, is indicated to shorten the duration of illness, to reduce the volume of intravenous fluid required and to cut down transmission of the disease. Doxycycline, a long acting tetracycline, given in a single dose was found to be as effective as multiple dose tetracycline in the management of adults with cholera. However, the results in adults may not be applicable to children. In this

study, we plan to compare single-dose doxycycline with the standard multiple dose tetracycline therapy in groups of actively purging children with cholera. Such single-dose therapy should have great practical importance in treating cholera patients, especially in settings with minimal resource or nursing supervision.

E. Methods of Procedure

Study design:

Inclusion and exclusion criteria

Patients with the following characteristics will be admitted in the study:

- male children,
- aged 3 to 12 years,
- with acute watery diarrhoea, with 3 or more watery stools in the last 24 hours,
- for less than 24 hours prior to admission in the study,
- with moderate to severe dehydration,
- with a stool dark-field examination positive for *V. cholerae*,
- with a stool output greater than 5 ml/kg/h measured during an initial observation period of 4 hours prior to selection for the study,
- not severely malnourished (wt. (kg) for ht.(cm) more than 70% of NCHS standard).

Patients with the following characteristics will be excluded from the study:

- marasmus or kwashiorkor,
- visible blood in the stool,
- serious concurrent illness (e.g. meningitis, pneumonia etc.) or a recognized chronic disease (e.g. tuberculosis),
- history of taking an antibiotic within three days prior to admission.

Sample size

In one previous study in patients with cholera on tetracycline treatment, the mean stool output was 269 ml/kg/episode with a standard deviation of 146 ml/kg/episode in the placebo group. (Moechtar A et al, unpublished, WHO funded study). Based on this study and expecting to detect 25% increase in total stool output with doxycycline therapy, a sample size of 75 in each treatment group will be required (80% power and a type 1 error = 0.05). Another fifteen patients will be added in each group for dropouts and deviated course of patient.

Informed consent and ethical review:

The legal guardians of the subjects involved in the study will be fully informed about the trial and their freely given consent for the subject to participate will be obtained in writing, by one of the investigators. The Nursing Officer or the on-duty nurse in the study ward will ascertain that the information given before obtaining consent is understood by the

parents or legal guardian.

The study shall commence only after being approved by the Ethical Review Committee of ICDDR,B.

Baseline examination:

A baseline history and physical examination will be obtained in order to determine the subject's eligibility for the trial and to collect relevant data that will allow comparison of the study groups after randomization. The baseline history and examination will include:

- identification of the patient (name, age, sex, address etc.)
- a description of symptoms prior to admission and their duration,
- a description of any treatment given for the illness before admission,
- feeding status prior to admission,
- a description of the stool,
- physical examination including the status of hydration and nutrition,
- results of stool dark-field examination for *V. cholerae*, stool microscopy, haematological and biochemical investigations done on admission.

Randomization:

The two treatment regimens will be

A - Single dose doxycycline - 5 mg/kg orally

B - Multiple dose tetracycline - 50 mg/kg orally in four divided doses for 3 days.

Identical in appearance, the preparations of the drugs will be provided by WHO. Each dose will be labelled separately, so that in case of the single dose doxycycline group, the drug will be in the first dose and starch placebos in the subsequent doses. Permuted blocks of constant length will be used in the randomization code. The code for the drugs will be kept at WHO head quarters and a sealed copy of the code will be sent to Dhaka to be kept in a locked cabinet for emergency use only. Randomization will take place after completion of the initial intravenous rehydration, just before administration of the drug. The code will be broken after the study has been completed and the data analysed according to groups.

Case management

An observation period of four hours for the patient starts when the patient is provisionally selected. Intravenous acetate or "Dhaka solution" will be infused to correct the dehydration during the initial 4 hours (until all clinical features of dehydration have disappeared). The composition of acetate solution is Na^+ 133 mmol/l, Cl^- 98 mmol/l, K^+ 13 mmol/l and the equivalent of

bicarbonate, in the form of acetate, 48 mmol/L. In case of severe dehydration, the infusion is given as 100 ml/kg within 4 hours. If the dehydration is moderate, the infusion is then given as 60-80 ml/kg, depending on the clinical condition of the patient. Weight will be taken before initial intravenous hydration. Stool output and the volume of intravenous fluid administered during this observation period will be carefully measured. A stool specimen will be obtained for dark field examination for *V. cholerae* during this period. It will be examined both directly and after 4 hours incubation (at 37°C) in alkaline peptone water. A presumptive report of *V. cholerae* is made if the darkfield examination reveals organisms with typical motility and if this motility is inhibited by *V. cholerae* antiserum.

At the end of initial rehydration during the observation period, if a patient is found to be eligible and his guardian gives the consent, he will be enrolled for the study. Randomisation will be done at this point and the first dose of the drug shall be administered. Rice-ORS will be given to all children as a volume to volume replacement for each diarrhoeal stool till cessation of diarrhoea , and the amount will be precisely recorded. Rice ORS, the standard oral rehydration solution at the CRC has the following composition - rice powder 50 g/l, Na^+ 90 mmol/l, Cl^- 80 mmol/l, HCO_3 30 mmol/l, and K^+ 20 mmol/l.

The patient will be weighed daily. Fluid intake stool and urine output measurements in millilitres will be made 8 hourly. The number of episodes of vomiting will be recorded. A stool specimen and a rectal swab specimen will be obtained on admission into the study ward and each morning during the study days for culture of *V. cholerae*, *Salmonella* and *Shigella*. For culture of *V. cholerae*, inoculation will be made in tellurite taurocholate gelatin agar both directly and after 6 hours' incubation in alkaline peptone water. *V. cholerae* will be reported if typical colonies are observed (gellatinase positive, tellurite positive and appeared translucent) that agglutinated in *V. cholerae* 01 antiserum. The isolates will be further characterized by agglutination with chicken red cells and by sensitivity to Polymixin B.

Finger pick samples of blood will be examined for haematocrit and plasma specific gravity on admission and subsequent 2 days to monitor the status of hydration.

All patients will be kept under close observation in the study ward until the diarrhoea has ceased for at least 24 hours and their faecal culture is negative for *V. cholerae* for 2 consecutive days.

"End of diarrhoea" will be defined as having occurred at the end of the last 8 hour period in which a liquid stool was passed.

A patient who passes soft or formed stool, thereby reaching "end of diarrhoea" and subsequently passes sufficient quantities of liquid stool to require resumption of either oral or intravenous fluid therapy, will be considered to have "clinically relapsed".

Patients who are bacteriologically negative on both direct and enrichment cultures for two days from treatment and then become subsequently positive, will be considered to have had a "bacteriological relapse".

Intravenous acetate solution will be infused to those patients during the maintenance phase (after initial I.V. rehydration and after the drug therapy has started), in whom clinical signs of moderate or severe dehydration reappear despite intake of the estimated ORS requirement or in whom uncontrollable vomiting does not permit ORS intake. This group of patients will constitute the "Unscheduled I.V. group".

Withdrawal from the study:

Reasons for withdrawing a patient from the study will be - non-compliance of the subject, either because the patient was removed from the study (e.g. withdrawal of informed consent, or because the patient required unscheduled treatment for a serious intercurrent illness .e.g. pneumonia, meningitis, etc.). Such patients will be given the standard treatment as the circumstances warrant. Data from these patients withdrawn will be included upto the time of withdrawal. Another analysis in which these patients are excluded will also be performed. Reasons for patient withdrawal will be precisely summarised.

Facilities and patient population:

Patients will be screened and observed in the observation ward of the centre. Upon being eligible for the study, they will be transferred to the study ward. The study ward has its own nursing staff. The number of beds cannot be kept reserved for our study. Patients with cholera usually report from Dhaka city and its suburbs. We hope to study 2 patients weekly but this will again depend upon the seasonal variation of cholera outbreaks.

Analysis of data:

Admission or pre-intervention data of the 2 groups will be compared with regard to the mean (also standard deviation) and median of age in months, duration of diarrhoea in hours prior to admission and stool output in ml/kg/h from admission into the hospital until the start of the intervention. Status of nurtition, dehydration and vomiting will also be compared. The response variables will be similarly compared between groups. 95% confidence intervals will also be determined for the major outcome variables. In case of asymmetric distribution of any data, log transformation may be used before analysis.

Statistical analyses will be done by t-test, Wilcoxon's rank sum test and Chi-squared test with statistical package for the social sciences (SPSS PC+).

Major response variables will be:

- Total stool output, in ml/kg of body weight, from the time of randomisation and initiation of treatment until the end of diarrhoea.
- Duration of diarrhoea, in hours, after randomization and initiation of treatment.
- Proportion of clinical relapses in each group.

Secondary response variables will be:

- Volume of ORS intake and water consumed during the first 24 hours after initiation of treatment, in ml/kg of body weight.
- Total volume of ORS intake and water consumed from initiation of treatment until diarrhoea stops, in ml/kg body weight.
- Frequency of vomiting in the first 24 hours after initiation of treatment.
- Proportion of unscheduled I.V. fluid therapy in each group.

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Diet schedule

Age group 1-2 years — Energy requirement - 1200 Kcal/d
*Protein " - 13.2 gm

Median body wt. - 11 kg

Daily food allocation	Prot/g	Energy/Kcal
Breast milk		
** Milk suji - 1000 ml	10.4	670
*** Khichuri - 400 gm	2.0	400
	12.4 gm	1070 Kcal

(Rest of the energy and protein are expected to come from breast milk).

* . In terms of egg or milk
** Milk sji is prepared with milk powder + Rice powder + Sugar Soya oil - Energy 67 Kcal/100 ml.
*** Khichuri - main ingredients are rice+dhal+chicken+oil - Energy 100 Kcal/100 gm.

Age group 2-5 years — Energy requirement - 1450 Kcal/d
Protein " - 18.0 gm/d

Median body wt. - 15 kg

Daily food allocation	Prot/g	Energy/Kcal
Milk suji - 1000 ml	10.4	670
Khichuri - 240 gm	1.0	240
~~Bread - 2 slice~~	~~-~~	~~120~~
Egg (boiled) - One	6.0	90
Cooked rice - 200 gm	-	240
Chicken/fish - 200 gm	10.0	100
Cooked mixed veg. - 200 gm	-	50
Cooked dhal - 100 gm	-	50
	27.4 gm	1560 Kcal

Age group 5-10 years

Energy requirement - 2000 Kcal/d
Protein " - 24.0 gm/d

Median body wt. - 24 kg

Daily food allocation	Prot/g	Energy/Kcal
Milk suji - 650 ml	13.5	650
Khichuri - 200 gm	1.0	200
Bread - 3 slice	-	180
Egg (boiled) - One	6.0	90
Cooked rice - 500 gm	-	600
Chicken/fish - 100 gm	10.0	100
Cooked mixed veg. - 400 gm	-	100
Cooked dhal - 200 gm	-	100
	30.5 gm	2020 Kcal

Age group 10-12 years(boys)

Energy requirement - 2300 Kcal/d
Protein " - 34.5 gm/d

Median body wt. - 34.5 kg

Daily food allocation	Prot/g	Energy/Kcal
Milk suji - 750 ml	15.5	750
Bread - 3 slice	-	180
Egg (boiled) - One	6.0	90
Cooked rice - 800 gm	-	960
Chicken/fish - 150 gm	15.0	150
Cooked mixed veg. - 400 gm	-	100
Cooked dhal - 200 gm	-	100
	36.5 gm	2350 Kcal

Food and water will be offered ad lib. Time of feeds offered will be accordance with the standard practice in the hospital.

SECTION III - BUDGET

1. Personnel services:

Name	Position	% of time	1st year (US$)	2nd year (US$)
Dr A.N. Alam	Principal Investigator	20%	-	-
Dr M.R. Islam	Co-Investigator	10%	-	-
Medical Officeer-1	"	25%	3300	3300
Trainee Research Fellows (Doctors) - 2		100%	4400	4400
Study volunteers - 4		100%	2400	2400
		Sub Total	= 10100	+ 10100

2. Drugs to be provided by WHO -

3. Laboratory tests:

HCT, Sp.gr.	268	200
R/S for Vibrio, Salmonnella, Shigella	1000	796
R/S for *V. cholerae* only (4 times)	2000	1430
R/S for D/F	300	162
Electrolytes and creatinine	1314	1000
Sub Total =	$ 4882	3588

4.	Hospitalization of patients (150 pts X 5 days X 30)	$ 17000	10000
5.	Transporation	200	200
6.	Printing & reporduction	200	200
7.	Glassware & others	200	100
8.	Stationaries	500	500
9.	Capital expenditure	300	-
10.	~~Data analysis~~	-	~~1200~~
	Total US$ =	33382	25888

GRAND TOTAL = US $ 59270.00

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. One hundred and eighty children between 3 to 12 years of age suffering from cholera of less than 24 hour duration and without recent history of taking antibiotics will be selected for the study. Patients with complications e.g. fever, pneumonia, meningitis, convulsion or severe protein energy malnutrition will be excluded from the study.

2. Any untoward reactions associated with therapy will be noted.

3. There is no potential risk involved in the study, every precaution will be taken to safeguard the interests of the patients. Although tetracycline use may cause staining of teeth in children, doxycycline has been shown to cause less of staining and a single dose of doxycycline hopefully will cause less of this side effect.

4. All records will be kept strictly confidential and will remain with the investigators.

5. Informed consent (signed or thumb impression) will be obtained from the parent/legal guardian of each patient enrolled in the study. There is no procedure in this study which may unmask the privacy of the subject.

6. Interview will be taken only related to the history of illness and is needed only for clinical management of the disease. Five minutes will be enough to take such a clinical history.

7. The patients will be benefit from the treatment of the diarrhoeal illness. General benefits to the society include the possible identification of a safe and economic drug for the treatment of cholera even in situations where minimal medical supervision is available.

8. No retrospective hospital records will be used. The study will require daily stool and rectal swab samples for bacteriological culture and examination of finger prick blood samples for HCT and specific gravity on admission and subsequent two days.

CONSENT FORM

The ICDDR,B provides treatment to patients suffering from cholera and other diarrhoeal diseases. It is also carrying out research to find the most economic, simple and effective way of treating cholera with antibiotics in addition to intravenous and oral rehydration fluids. Drugs used conventionally, such as furazolidone, have lost their effectiveness against cholera. A single dose of doxycycline has been proved to be effective against cholera in adults, although tetracycline given in multiple doses still remains the drug of choice. We would like to compare the efficacy of a single dose doxycycline, in a dose of 5 mg/kg, with a multiple dose course of tetracycline, in a dose of 50 mg/kg/day, for 3 days in children between 3-12 years suffering from severe cholera. These drugs are known to cause staining of teeth in children, but the chances of staining are very negligible with such a short course of treatment. A single dose of doxycycline, if found to be as good as a multiple dose course of tetracycline, will be the most simple and economic treatment regimen in cholera. We would like your child to participate in this study.

If you are willing to have your child included in the study, you can expect that:

1. Your child shall have to stay in the hospital for about 5 days.

2. Daily rectal swab tests will be done to determine how long the germ for cholera remains in the stool.

3. Finger stick blood will be examined for haematocrit and specific gravity on the first 3 days.

4. Your child will receive the standard medical care during his stay in the hospital.

5. Your child shall receive either the single dose doxycycline or the multiple dose tetracycline treatment in addition to the intravenous and oral rehydration fluids.

Even if you may not want your child to take part in the study, he will be provided the standard treatment. Moreover, you may withdraw your child from the study at any time and your child will still receive the same standard treatment for his/her illness.

If you are willing to have your child included in this research work, then please give your signature below or the impression of your left thumb.

----------	----------
Signature of investigator	Signature or LTI of guardian/ parent
----------	----------
Signature of witness	Name of the patient

Date: ----------

সম্মতি পত্র

কলেরা ও অন্যান্য ডায়রিয়াতে আক্রান্ত রুগীদের চিকিৎসার জন্য আই সি ডি ডি আর, বি নিয়োজিত। কলেরা চিকিৎসায় অন্তঃশিরায় ও মুখে খাবার স্যালাইনের ব্যবহার ছাড়াও একটি সুলভ, সহজ ও কার্যকরী এন্টিবায়োটিক আবিষ্কারের প্রচেষ্টা চলছে। সনাতন ব্যবহৃত ওষুধ, যেমন ফিউরাজলিডোন, কলেরার বিরুদ্ধে কার্যকারীতা হারিয়ে ফেলেছে। টেট্রাসাইক্লিন একাধিক মাত্রায় এখনও কলেরার জন্য উত্তম ওষুধ; তবে বয়স্কদের ক্ষেত্রে একমাত্রা ডক্সিসাইক্লিনও সমান কার্যকর বলে প্রমানিত হয়েছে।

আমরা মারাত্মক কলেরায় আক্রান্ত ৩ থেকে ৯২ বছর বয়স পর্যন্ত শিশুদের ক্ষেত্রে একমাত্রা ডক্সিসাইক্লিন ও একাধিক মাত্রা টেট্রাসাইক্লিন ওষুধ প্রয়োগের কার্যকারীতা তুলনা করতে চাই। এক মাত্রা ডক্সিসাইক্লিনে থাকবে ৫ মিঃগ্রাঃ/কেজিঃ শরীরের ওজন এবং একাধিক মাত্রা টেট্রাসাইক্লিনে থাকবে ৫০ মিঃগ্রাঃ/কেজিঃ, যা ৩ দিন ৬ ঘন্টা পর পর সেবন করতে দেয়া হবে। ঐ সকল ওষুধ সেবনে শিশুদের দাঁতের রং পাল্টাতে পারে। কিন্তু এত স্বল্প দিনের চিকিৎসায় এই পার্শ্ব প্রতিক্রিয়ার সম্ভাবনা অত্যন্ত নগন্য। যদি মাত্র এক মাত্রা ডক্সিসাইক্লিন একাধিক মাত্রা টেট্রাসাইক্লিনের মতই কার্যকর প্রমানিত হয়, তাহলে এই ওষুধি কলেরা রোগের জন্য একটি সহজ ও সুলভ চিকিৎসা হিসাবে বিবেচিত হবে। আমরা আপনার শিশুকে এই গবেষনায় অংশগ্রহন করাবার জন্য অনুরোধ জানাচ্ছি।

গবেষনায় অংশ গ্রহনে ইচ্ছুক হলে নিম্নলিখিত কাজ আপনার শিশুর ক্ষেত্রে প্রযোজ্য হবে ঃ

১. আপনার শিশুকে হাসপাতালে আনুমানিক ৫ দিন থাকতে হবে।
২. কলেরার জীবানু কতদিন শিশুর মলে থাকে, তা দেখার জন্য শিশুর মলদ্বার থেকে কাঠির সাহায্যে সোয়াব নিয়ে পরীক্ষা করা হবে।
৩. প্রথম ৩ দিন শিশুর আঙ্গুল থেকে রক্ত নিয়ে হিমাটোক্রিট ও আপেক্ষিক গুরুত্ব পরীক্ষা করা হবে।
৪. আপনার শিশু হাসপাতালে থাকা অবস্থায় উপযুক্ত চিকিৎসা পাবে

৫. খাবার ও শিরায় দেয়ার স্যালাইন ছাড়া আপনার শিশুকে একমাত্রা ডক্সিসাইক্লিন অথবা একাধিক মাত্রা টেট্রাসাইক্লিন ওষুধ দেয়া হবে।

গবেষনায় অংশ গ্রহণে ইচ্ছুক না হলেও আপনার শিশুকে হাসপাতালে প্রয়োজনীয় সকল চিকিৎসা দেয়া হবে। উপরন্তু, গবেষনা চলা অবস্থায় আপনি যে কোন সময়ে আপনার শিশুকে গবেষনা থেকে সরিয়ে নিতে পারেন। সে ক্ষেত্রেও আপনার শিশুকে উপযুক্ত চিকিৎসা দেয়া হবে।

আপনি এই গবেষনায় আপনার শিশুকে অংশ গ্রহন করাতে ইচ্ছুক হলে দয়া করে নিম্নে আপনার স্বাক্ষর অথবা বাম বৃদ্ধাঙ্গুলির ছাপ দিন।

গবেষকের স্বাক্ষর

অভিভাবক অথবা পিতা/মাতার স্বাক্ষর/বাম বৃদ্ধাঙ্গুলির ছাপ

সাক্ষীর স্বাক্ষর

রোগীর নাম:

তারিখ:

ANSWER TO REVIEWER'S COMMENTS:

Reviewer one:

1. Children who have taken antibiotics with three days prior to admission will be excluded.

2. Yes, a separate analysis will be done on patients who will drop out or be withdrawn from the study. Additional twenty patients will be included in the study for any deviated course.

3. Sample size determination has been done considering the reviewers concern and valuable comments. In consultation with our statistician, Dr Bairagi, 70% increase in the trial size has been proposed for 80% power.

4. No, starch in small amount has not been shown to have antidiarrhoeal effect.

5. Yes, all I.V. rehydration will be done in the study ward.

6. Yes, the patients will be retained until faecal culture is negative for two consecutive days.

7. About 7% patients had therapeutic failure in the previous study. End point of diarrhoea is defined for analysis.

Reviewer Two

- No, the study cited in reference no. 9 was performed in 160 children aged 6 to 12 years.

- Dose of doxycycline should be 5 mg/kg body weight and the typing error has been corrected.

- Stratification may not be necessary as all our patients will initially have I.V. rehydration.

- Sample size determination: has already been discussed.

Reviewer Three

No major comment has been made.

Reviewer (1)

Title: Randomized double-blind trial of single dose doxycycline treatment of cholera in children

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project		✓	
Adequacy of Project Design			✓
Suitability of Methodology		✓	
Feasibility within time period	No accrual estimates given		
Appropriateness of budget		✓	
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☐

b) with qualification

- on technical grounds ☑
- on level of financial support ☐

I do not support the application ☐

OK Allan. Since this came via fax seems like the words have not come clearly. Louis

... double blind trial of single dose doxycycline in the treatment of cholera in children

Reviewer [redacted] FAX

010 880 2 883116

Comment

Abstract Confusion between 140 subjects and 2 × 75 = 150 cases

Methods ✓1 Why exclude children who have taken antibiotics within 1 week?

✓2 Patients who drop out

(i) by choice — record intake/output/excretion of V. chol until time of discharge. Include in analysis

(ii) medical complication — as above until follow-up to discharge, or to time of medical complication if study measurements would distress patient

(iii) culture negative — reason in analysis. Perhaps some cases is consistency on [redacted] specified dark-field stool examination.

(iv) patient replacement — NO. Allow additional 10%. Study size for difficulties (i) - (iii) which may weaken discrimination between treatments

3 Sample size is gross underestimate. This is effectively an equivalence trial. If duration of stool output was 40% longer with doxycycline would you really abandon tetracycline? Trial target of 30% seems more appropriate; given that you are prepared to make some exception on duration of illness for the convenience of single dose. Figure 70% increase in proposed trial size for 80% power in respect of 30% reduction in stool output. What about V. cholerae?

4 Is 'starch' a genuine placebo. Does it have anti-diarrhoeal properties?

cane IV rehydration not be given in the study ward (a
study measurements continued?)
patients be retained until "faecal culture is negativ
cholerae for two consecutive days?"
at % therapeutic failures are detected on the two trea
x define this endpoint modified for analysis purposes?
x analysis, why is there not corresponding power calc
under constant for "bacteriological relapse"

Reviewer (2)

Title: Randomized double-blind trial of single dose doxycycline in the treatment of cholera in children

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project		X	
Adequacy of Project Design		X	
Suitability of Methodology	X		
Feasibility within time period	X		
Appropriateness of budget	X		
Potential value of field of knowledge	X		

CONCLUSIONS

I support the application:

a) without qualification /__/

b) with qualification

- on technical grounds /X/
- on level of financial support /__/

Thank you for asking me to review the research protocol "Randomized Double Blind Trial of Single Dose Doxycycline in the Treatment of Cholera in Children" that has been proposed for study at ICDDR,B. I reviewed the protocol in detail and believe that, if successfully completed, it will provide valuable practical information that will be quite useful in the treatment of cholera in children. I do have some specific comments.

I assume that the study cited in reference #9 was performed in adults. There appears to be some inconsistencies in the protocol regarding the actual dose of doxycycline that will be employed. In the summary on page 2 the doseage was given as 4.5 mg/kg, while on page 7 the dose was 5 mg/kg. This should be resolved.

Consideration should be give to the possibility that there should be stratification of the two groups into those individuals requiring initial intravenous hydration and those who do not. It is possible that doxycycline would be more effective in individuals requiring intravenous hydration which, I would presume, would be indicative of a more severe bout of cholera.

I have some comment regarding the sample size that is discussed on page 7. I believe that the present determination attempts to avoid a type 1 error and estimates the sample size necessary to identify the effect of an active agent to decrease stool output (vs placebo control). However, in this study design in which two potentially active agents are being compared (without a placebo group), and the major statistical need is to exclude a type 2 (or beta) error. This is critical since, as I understand the study design, these investigators hope to establish that doxycycline is comparable to tetracycline. Such an observation would be established if there is no difference in the ability of these two antibiotics to reduce stool output. As a result, a power calculation must be done to establish the appropriate sample size to avoid a so-called type 2 (or beta) error.

I am not able to provide an adequate assessment of the appropriateness of the budget in that major budget items are attributed to certain categories while other categories (which in my experience usually are quite expensive) are relatively minor charges.

In conclusion, this is an appropriate study which should be performed. I am certain that a discussion with your consulting statisticians - regarding the sample size and the type 2 error should resolve the concerns that I have raised.

Thank you for asking me to review this protocol. As you know, I am always very pleased to help advance the goals of ICDD,B. I look forward to seeing you during the coming year. My very best wishes for the New Year.

Sincerely,

Reviewer (3)

Title: Randomized double-blind trial of single dose doxycycline in the treatment of cholera in children.

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project	✓		
Adequacy of Project Design	✓		
Suitability of Methodology	✓		
Feasibility within time period	✓		
Appropriateness of budget	✓		
Potential value of field of knowledge	✓		

CONCLUSIONS I hope this will complete the evaluation of single dose doxycycline. I'm curious to know if adults are now treated routinely + doxy at ICDDRB.

I support the application:

a) without qualification ☒

b) with qualification

- on technical grounds ☐
- on level of financial support ☐

I do not support the application ☐

n. in D.

iewer: JJ Jack.

Excellent protocol - hopefully the last in a line of studies on dogs. It will be nice to finally stop testing this subject to rest... but not until after this study is complete.