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Date 23/9/1985

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. A.N. Alam

Application No. 85-031

Title of Study Single-dose Doxycycline in the Treatment of Cholera.

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)

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

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes (No)
   (c) Minors or persons under guardianship — Yes (No)
2. 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)
3. 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
4. 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.

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

A Alam
Principal Investigator

Trainee

85-031
24/9/85

SECTION I - RESEARCH PROTOCOL

1. TITLE: SINGLE-DOSE DOXYCYCLINE IN THE TREATMENT OF CHOLERA

2. PRINCIPAL INVESTIGATOR: Dr A.N. Alam

   CO-INVESTIGATORS: Dr N.H. Alam

   Dr T. Ahmed

   CONSULTANT: Dr D.A. Sack

3. STARTING DATE: Nov 1, 1985

4. COMPLETION DATE: May 31, 1986

5. DIRECT COST: US $ 21,251.00

6. SCIENTIFIC PROGRAMME: This protocol has been approved by the Pathogenesis and Therapy Working Group

Signature of the Programme Head

Date: [signature]

7. ABSTRACT SUMMARY:

A randomized double blind prospective controlled study will be carried out on 150 adult patients with proven cholera to compare the relative efficacy of single dose doxycycline with tetracycline in the treatment of cholera. Patients will be divided into three equal groups of fifty patients each who will receive either single dose of 200 mg or a single dose of 300mg of doxycycline orally given on the first day of hospitalization or multiple doses of tetracycline (500 mg 6 hourly for 2 days). All patients will receive I.V. rehydration therapy followed by oral maintenance hydration. Success of therapy

will be determined by comparing purging and rehydration volumes at 8 hourly intervals, and by comparing the duration 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 patient compliance and simplify logistics in treating cholera patients, especially in field situations or during epidemics.

8. REVIEWS:

(a) Ethical Review Committee: _____

(b) Research Review Comittee: _____

(c) Director: _____

SECTION II - RESEARCH PLAN

A. Introduction:

1. Objectives

To compare the efficacy of a single-dose doxycycline (either 200 or 300 mg) with the standard multiple doses of tetracycline in patients with cholera.

2. Background Information:

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 and duration of diarrhoea and the excretion of vibrio 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). 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 (3, 4) or over a period of four days (5). 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 (4, 6). 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 an dose is absorbed. With a half life of 15-20 hours, therapeutic plasma level persist 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) and can be avoided by giving with or after food. A disadvantage of doxycycline is its increased cost relative to tetracycline. Recently, however, the price has been decreasing because the patent has expired.

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. Although several studies have demonstrated the efficacy of both single and multiple dose doxycycline, no single study has directly compared the antibiotic treatment options nor evaluated the degree to which nausea might interfere with higher dose (300 mg) doxycycline therapy. Because of the need for this direct comparison, the World Health Organization has requested ICDDR,B to carry out this study.

B. Rationale:

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

C. Specific Aims:

Compare the clinical and bacteriologic efficacy of doxycycline in single doses of 200 mg or 300 mg with multiple doses of tetracycline (500 mg 6 hourly for 2 days) in a controlled trial of adult patients with cholera.

D. METHODS AND PROCEDURE:

Selection of patients:

One hundred fifty adults above 15 years of age with clinical history of acute watery diarrhoea with <24 hours duration,

evidence of >5% dehydration and a stool dark-field examination positive for V. cholerae will be eligible for the study. Patients to be excluded will be those who had taken antibiotic within one week of hospitalization, pregnant women and those with other systemic illnesses. Patients who drop out of the study, either by choice, because a medical complication develops or because the initial culture was negative will be replaced by additional patient.

Patients who are potentially eligible will be rehydrated with standard I.V. solution (Dhaka solution) then maintained with ORS (glucose) and will be observed for four hour observation period. Consenting patients whose purging rate is ≥ 20 ml/kg during the four hours basal period will be transferred to the study ward and will be assigned to one of three treatment regimens. Glucose ORS will be used to replace diarrhoea stool losses and patients will be fed simple foods on entry into the study ward (rice, bread, banana). The three treatment regimens will be:

A- Single dose doxycycline - 200 mg

B - Single dose doxycycline - 300 mg

C - Multiple dose tetracycline - 500 mg Q6HR x 8

Determination of Sample size

Three previous studies with similar patients showed mean stool outputs of 250ml/kg/episode (1,3,4) with a standard deviation of about 100ml/kg/episode. Based on these studies, we estimate that a sample size of 50 per group will provide significantly different

mean purging rates if the output difference between groups is $\geq$ 50 ml/kg/episode (at 95% level of confidence, an alpha value of 0.05 and beta value of 0.20).

Randomization and Drug Administration:

Preparations of the drugs are being provided by WHO with identical appearing capsules for each antibiotic group. Each dose will be labelled separately so that, in the case of the single dose doxycycline groups, the drug will be in the first dose and a starch placebo will be given in subsequent doses.

The drug will be provided with patient numbers from 1-180 with drugs randomly assigned between the 3 groups using block randomization. The code for the drugs will be kept at WHO headquarters and a sealed copy of the code will be sent to Dhaka to be kept in a locked cabinet for emergency use only.

The capsules will be given on admission to the study ward, after the patients have been hydrated and have taken some food. All patients will be carefully monitored daily for any side-effect.

Clinical management and data collection:

In addition to the antibiotic therapy (above), and I.V. hydration therapy, patients will be allowed food and water ad lib. Weights will be taken on admission and daily.

Intake and output measurements will be made 8 hourly. The numbers of episodes and volume of vomiting following admission to the study ward will be carefully determined.

Any patient developing systemic complications or excessive vomiting where I.V. rehydration had to be reinstituated will be transferred to the general ward and treated accordingly.

A stool specimen will be obtained on admission for darkfield exam and for culture of V. cholerae, salmonella and shigella. A rectal swab specimen will be obtained each morning only for V. cholerae culture. The specimens for darkfield exam will be examined both directly and after 4 hours incubation (37°C) in alkaline peptone water. A presumptive report of V. cholerae is made if the darkfield exam reveals organism with typical motility and if this motility is inhibited by anti V. cholerae antisera.

For vibrio culture we will innoculate TTGA 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, translucent) which agglutinate in V. cholerae 01 antiserum. The isolates will be further characterized by agglutination with specific antisera and by agglutination with chicken red cells and sensitivity to Polymixin B.

All patients will be kept under close observation in the hospital until the diarrhoea has ceased for at least 24 hours and their faecal culture is negative for V. cholerae for two 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 intravenous fluid therapy, will be considered to have "clinically relapsed". Any patient in whom diarrhoea lasted longer than 48 hours from the start of treatment will be considered to be a "therapeutic failure".

Patients will be termed bacteriologically positive if either direct plate or culture from alkaline peptone water from rectal swabs isolate V. cholerae. Patients who are bacteriologically negative on both direct and enrichment cultures for two days from treatment and then becomes subsequently positive, will be considered to have had a "bacteriological relapse".

Finger stick blood will be examined for haematocrit and specific gravity on admission and subsequent 2 days to determine the degree of dehdyration.

Analysis of data:

We will compare:

a) Comparability on admission

b) Purging volumes

c) Duration of purging

d) Duration of stool culture positivity for *V. cholerae*

e) Treatment failure rates

f) Bacteriological relapse rate

Comparison of purging rates is tested using Student's "t" test and failure rates are compared using Chi-square analysis.

SECTION III - BUDGET

1. PERSONNEL SERVICES

Name	Position	% of effort	US Dollar
Dr A.N. Alam	Principal Investigator	20%	1000.00
Dr N.H. Alam	Co-Investigator	20%	400.00
Dr. T. Ahmed	=do=	20%	300.00
Dr D.A. Sack	Consultant	5%	-
3 Staff Nurse (Study ward)		20%	900.00
1 Clerk -	"	20%	180.00
3 Cleaners -	"	20%	360.00
		Sub Total:	3140.00

2. Supplies and Materials (Antibiotics provided by WHO)	..	
3. Laboratory Tests:		
HCT, Specific gravity	..	795.00
Rectal swab for culture (Vibrio, Salmonella, Shigella etc).	..	2,431.00
4. Equipment	..	Nil
5. Hospitalization of patients 160x5xTk.500) day	..	14,285.00
6. Outpatient care	..	
7. ICDDR,B transport	..	Nil
8. Transportation of Materials	..	Nil
9. Rent, Communication, Utility	..	100.00
10. Printing & Reproduction	..	500.00
11. Contractual service	..	Nil
12. Construction	..	Nil
	Sub Total:	21,251.00

Indirect Costs (31%) $6,588.00

GRAND TOTAL: US$ 27,839.00

REFERENCES

1. Lindenbaum, J., Greenough W.B.III, Islam, M.R. 1967. Antibiotic Therapy of cholera, Bull. WHO 36:871-883.

2. Wallace, C.K., Anderson, P.N., Brown, T.C., Khanra, S.R., Lewis, G.W., Pierce, N.F., Sanyal, S.N., Segre, C.V., Waldman, R.H. 1968. Optimal antibiotic therapy in cholera. Bull. WHO 39: 239-245.

3. Sack, D.A., Islam, S., Rabbani, H., Islam. R. 1978. Single dose doxycycline for cholera. Antimicrob. agents chemother. Sept. 14:462-64.

4. De, S., Chaudhuri, A., Dutta, D., De S.P.,and Pal. S.C. 1976. Doxycycline in the treatment of cholera. Bull. WHO 54:177-179.

5. Rahaman, M.M., Majid, M.A., Alam, A.K.M.J.,and Islam. M.R. 1976. Effects of doxycycline in actively purging cholera patients: a double blind trial. Antimicrob. Agents Chemother. 10: 610-612.

6. McMormack W.M., Choudhury, A.N., Jahangir, N.,A. Ahmed, A.B.F., and Mosley, W.H. 1968. Tetracycline Prophylaxis in families of cholera patients. Bull. WHO (68) 38: 787.

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. One hundred and twenty adult patients (above 15 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. Pregnant women or patients with complications e.g. fever, pneumonia, 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 patient.

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 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 benefit from the treatment of 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 rectal swab for bacteriological culture and exmination of finger stick blood for HCT and specific gravity on admission and subsequent two days.

CONSENT FORM

(SINGLE DOSE DOXYCYCLINE IN THE TREATMENT OF CHOLERA)

(Statement to be read to the patient when consent is obtained)

The ICDDR,B is carrying out research to find the most economic and effective way to treating cholera with antimicrobial agents in conjunction with intravenous and oral rehydration fluid. Doxycycline has been proved to be an effective drug against cholera, although tetracycline remains the drug of choice. We like to compare the efficacy of single-dose doxycycline in doses of 200 or 300 mg with a standard multiple dose course of tetracycline and a treatment without antibiotic in patients with cholera. Single dose of 200 mg doxycycline, if found to be as effective as single dose of 300 mg doxycycline or multiple doses of tetracycline, this will be the most rational and economic therapeutic regimen. We would like you to participate in this study for the benefit of society.

If you are willing to participate in the study, you can expect that:

1. You will receive the standard medical care during your stay in the hospital.

2. You will have to stay in the hospital for about 5 days till the completion of the study.

3. During your stay, daily rectal swab will be taken to determine how long the Vibrio remains in the stool.

4. Finger stick blood will be examined for hematocrit and Specific gravity on the first three days.

You do not have to participate in this study if you do not want to, still you will be treated like any other patient in this hospital. Moreover, you may withdraw from this study at any time without penalty.

The records of your treatment will be kept confidential.

If you wish to participate in the study voluntarily, then please sign your name or give left thumb impression below.

_____
Signature of Investigator

_____
Signature/Left thumb impression of patient.

Date:_____

সম্মতি পত্র

আন্তর্জাতিক উদরাময় গবেষনা কেন্দ্র স্বল্প ব্যয়ে ও কার্যকরী উপায়ে কলেরার চিকিৎসার জন্য খাবার স্যালাইন ও শিরায় স্যালাইনের সাথে সাথে এন্টিবায়োটিক দ্বারা চিকিৎসা উদ্ভাবনের জন্য গবেষনা চালিয়ে যাচ্ছে। ডক্সিসাইক্লিন কলেরা চিকিৎসায় একটি কার্যকরী ঔষধ প্রমানিত হয়েছে, যদি ও টেট্রাসাইক্লিন সবচেয়ে বেশী কার্যকরী এন্টিবায়োটিক হিসেবে প্রতিষ্ঠিত। আমরা প্রাপ্ত বয়স্কদের উপর একমাত্র বিভিন্ন পরিমানের ডক্সিসাইক্লিনের সাথে বহুমাত্রার টেট্রাসাইক্লিনের ও শুধু স্যালাইন দ্বারা চিকিৎসার তুলনামূলক গবেষনা করতে চাই। এই গবেষনার ফলে একমাত্রায় কম পরিমানের ডক্সিসাইক্লিনের কার্যক্ষমতা বেশী পরিমানের ডক্সিসাইক্লিন বা বহুমাত্রার টেট্রাসাইক্লিনের মত একই রকম বিবেচিত হইলে তটা স্বল্প ব্যয়ে কলেরা চিকিৎসার সহায়ক হবে ।

আপনি যদি দয়া করে এই গবেষনায় অংশ নিতে রাজী হন তবে আপনাকে নীচে লেখা ব্যবস্থাগুলোর মধ্যে যেতে হবে :-

১। হাসপাতালে থাকাকালে আপনার চিকিৎসার উপযুক্ত ব্যবস্থা করা হবে ।

২। গবেষনা চলাকালে প্রায় পাঁচদিন একনাগাদ আপনাকে হাসপাতালে থাকতে হবে।

৩। কতদিনে আপনার মল কলেরার জীবানুমুক্ত হচ্ছে তা দেখার জন্য প্রতিদিন আপনার গুহ্যদ্বার হতে সোয়াব নিয়ে পরীক্ষা করা হবে । হাসপাতালে থাকাকালে প্রথম তিন দিন পরীক্ষার জন্য আপনার আঙ্গুল থেকে কয়েক ফোঁটা রক্ত নিতে হবে। রক্ত নেবার সময় আপনি সামান্য ব্যথা অনুভব করবেন।

এই গবেষনায় যোগ দেওয়াতে আপনার কোন বাধ্য বাধকতা নেই। আপনি এতে যোগ না দিলেও আপনার চিকিৎসার ত্রুটি হবেনা । ইচ্ছা করলে গবেষনা চলাকালে-ও যে-কোন সময় আপনার সম্মতি প্রত্যাহার করতে পারেন। এতে করে আপনার হাসপাতালে প্রচলিত সুচিকিৎসার কোন ত্রুটি হবে না । যদি আপনি স্বেচ্ছায় এই গবেষনায় অংশ নিতে রাজী থাকেন অনুগ্রহ করে ,এখানে আপনার টিপসহি বা স্বাক্ষর দিন ।

গবেষকের স্বাক্ষর

রোগীর স্বাক্ষর/টিপসহি