Date 27 Nov. 1983

ETHICAL REVIEW COMMITTEE, ICDDR,B.

ncipal Investigator Dr. M.R. Islam

olication No. 83-042

le of Study "Single dose furazolidone in 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)

rcle 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

SECTION 1 - RESEARCH PROTOCOL

1.	TITLE:	SINGLE DOSE FURAZOLIDONE IN CHOLERA.
2.	PRINCIPAL INVESTIGATOR:	Dr. M. R. Islam
	CO-INVESTIGATOR:	Dr. T. Butler
3.	STARTING DATE:	January 1984
4.	COMPLETION DATE:	June 1984
5.	TOTAL INCREMENTAL COST:	US $ 20,360.00
6.	SCIENTIFIC PROGRAMME:	This protocol has been approved by the Pathogenesis & Therapy Working Group.

Signature of Scientific Program Head: T Butler

Date: 27 Nov 83

7. ABSTRACT SUMMARY:

A double blind, randomized and placebo controlled study is planned to findout the efficacy and safety of single dose Furazolidone in both adults and children suffering from cholera. 150 (75 adults and 75 children) cholera patients will be studied. Adults will receive one of the three treatment schedules (a) Single 400 mgm Furazolidone (b) Single one gm Tetracycline or (c) Single dose Placebo. Children will receive one of the four treatment schedules (a) Single dose Furazolidone 10 mgm/kg (b) Furazolidone 10 mg/kg/day in 4 divided doses daily for 3 days or (c) some placebos will be given as single doses and others for 3 days. All patients will be treated with intravenous fluid only. Effect of therapy of these different treatment schedules will be compared to find out an effective, less expensive but easy to administer drug regimen. If single dose Furazolidone therapy is found to be effective in cholera for both adults and children, then beside the advantage of the least possible risk of drug resistancy, the cost of the durg therapy will be reduced to half and thus will be very much benificial to the developing countries where cholera is endemic.

8. REVIEWS:

(a) Research involving human subjects: _____

(b) Research Review Committee: _____

(c) Director: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION:

1. Objectives:

To compare (i) clinical efficacy (ii) bacteriological eradication of V. cholerae (iii) clinical and/or bacteriological relapse (iv) "carrier" of V. cholerae when treated with:

(a) Single dose Furazolidone or single dose Tetracycline or Placebo in adults.

(b) Single dose Furazolidone or multiple dose Furazolidone or Placebo in children below age 8 years.

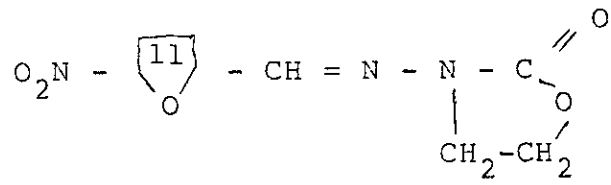
2. Background:

Cholera is one of the killing diarrhoeal disease in many developing countries, caused by V. cholerae. Several clinical trials have shown that Tetracycline reduces the duration of diarrhoea as well as duration of vibrio excretion, thereby diminishing the total amount of intravenous or oral rehydration fluid requirement (1,2). Controlled clinical trials with different dose schedules of tetracycline have shown that the duration of diarrhoea and duration of positive

culture for V. cholerae were significantly less than the patients treated without antibiotics. Increasing the dose tetracycline to 2-3 times from the standard therapeutic dose did not appear to enhance its therapeutic action. Therapeutic failures occured in patients treated with one day as well as in those treated with 4 days (1,2). In an attempt to develop a simplified low cost treatment schedule in cholera we carried out a randomized prospective clinical trial on 75 adult patients. Equal number of patients were studied in three types of treatment schedule consisting single one gram dose, two gram multiple dose divided 6 hourly over 24 hours and control (without antibiotic). No difference observed between the groups receiving either single dose or conventional multiple dose for the volume of intravenous fluid requirement, amount of purging and duration of diarrhoea ($p > .05$). These values were highly significant when compared to control group. 64% and 88% of cholera patients became vibrio free at the end of 24 and 48 hours respectively after single dose Tetracycline therapy where as only 24 % and 28 % respectively, vibrios could not be isolated in stool culture in the control group. Only 12% patients had bacteriological relapse after single dose therapy which was consistant with other comparison group. Thus low cost single dose tetracycline therapy was found to be as effective as conventional multiple dose therapy in cholera (3). Single dose tetracycline therapy also found to effective in acute Shigellosis (4,5).

Pharmacology of Furazolidone:

Furazolidone, a derivative of nitro-furan possesses antimicrobial activity. The structural formula of Furazolidone is:



(3- (5-Nitrofurfurylideueamino) - 2 - Oxazolidinone)

It is yellow, odourless, tasteless, crystalline powder and practically insoluble in water. The mechanism of the antibacterial activity of furan derivatives is unknown but it is presumed that the compound interferes with enzymatic process essential to bacterial growth. Heavy innocula of micro-organism reduces the activity of the drug. Bacteria develop only a limited resistance to furan derivatives and cross resistance between these compound and sulfonamides or antibiotics does not occur.

The most common untoward effects are anorexia, nausia, vomiting and diarrhoea. The incidence is less if the drug administered with food. Hypersensative reactions like fever with chill, leucopenia, granulo-cytopenia, haemolytic anaemia, cholestatic jaundice and hepatocellular damage, interstial pulmonary fibroses and polyneuropathis etc have been reported with nitrofurantion treatment but no such serious reactions have been reported with Furazolidone.

Pierce, Bunwel, Mitra et al in a controlled comparison of Furazolidone and Tetracycline have found that Furazolidone reduced total stool volume by 50% and duration of diarrhoeas by 40% when compared with control group receiving no antibiotics. They have used tetracycline 500 mgm 6 hourly X 48 hours, furazolidone 200 mgm every 6 hours for 72 hours, furazolidone 400 mgm daily for 3 days (3 doses)and a control group receiving no antibiotics (6). They have observed that Furazolidone significanty less effective than Tetracycline in rapidity of the eradication of vibrio cholerae. Chowdhury RN, Neogy KN, Sanyal SN et al have compared Furazolidone 100 mgm 6 hourly, 400 mgm once a day and tetracycline 250 mgm 6 hourly for 3 days in 3 groups of adult cholera patients and observed that Furazolidone and Tetracycline were equally effective in reducing the duration of diarrhoea,vibrio excretion and intravenous fluid administration. Also Furazolidone 400 mgm in a single daily dose for 3 days was as effective as 100 mgm 6 hourly multiple dose without any untoward effects (7).
Karchmer AW, Curlin G, Hoq MI et al also found that Furazolidone in doses of 5 mgm/kg/day for 7 days was as effective as Tetracycline in the treatment of pediatric cholera in reducing the volume and duration of diarrhoea and only slightly less effective in reducing the duration of vibrio excretion (8).

Guha Mazumder et al in a clinical trial comparing Furazolidone 100 mgm 6 hourly for 3 days with Tetracycline, Minocycline and no antibacterial agent, observed that Furazolidone appeared to be less effective than Tetracycline or Minocycline to eradicate V. cholerae. However, development of carrier state was found to be much lower in the furazolidone treated group (5.9%) than those treated by tetracycline (21.4%) (9).

C. METHODS AND PROCEDURE:

1. Patients selection:

Two groups of patients preferably male will be selected. Adult over 8 years and children below 8 years, will be considered for the study. 75 adults, 25 in each group of single dose Furazolidone, single dose Tetracycline or Placebo will be studied. 75 children, 25 in each group of single dose Furazolidone, or multiple dose Furazolidone or Placebo (some placebo will be given as single doses and others for 3 days). All patients will be treated with intravenous fluid only. Patient should have recent history of diarrhoea and vomiting (< 24 hrs). All suspected cases who attend ICDDR,B treatment centre will be screened by dark field microscopic examination of stool for *V. cholerae*. Only dark-field positive cases whose base line purging during 1st 4 hours observation is more than 20 ml/kg will be selected for the study.

2. Randomization:

Patients will be given serial numbers in the order they are selected for the study. From a table or random numbers the patient will be assigned to one of the three groups for adults and to one of the three groups for children.

3. Treatment schedule:

150 (75 adults and 75 children) cholera patients will be studied. Adults will receive one of the three treatment schedules (a) Single 400 mgm Furazolidone (b) Single one gm Tetracycline or (c) Single dose Placebo. Children will receive one of the four treatment schedules (a) Single dose Furazolidone 10 mgm/kg (b) Furazolidone 10 mg/kg/day in 4 divided doses daily for 3 days or (c) same placebos will be given as single doses and others for 3 days. All patients will be treated with intravenous fluid only.

4. Informed consent:

Selected patients or their legal guardians preferably parents in case of children will be explained the nature of the study and the alternative course for not enrolling. Those voluntarily agree to participate in the study will be asked to sign the informed consent. The inform consent will be printed in both Bengali and English languages.

5. Clinical data:

All patients will be admitted in the study ward of ICDDR,B where specially trained nurses and paramedics take care of the patients under the supervision of Principal investigator or Co-investigators. Since this will be a double blind randomized placebo controlled study there will be little biasness. The effect of treatment will be evaluated by fixed criteria like objective

measurements of weight, vital signs, duration of diarrhoea, the volume of stool output and duration of bacteriological vibrio positive cultures. All these measurements will be made at periodic intervals (every 8 hours) for each patient.

End of diarrhoea will be defined as having occured at the end of the last 8 hour period in which a liquid stool was passed. If a patient passes semisoft or formed stool or no stool for 24 hours, thereby reaching "end of diarrhoea" and subsequently passed sufficient quantities of liquid stool to require resumption of intravenous fluid therapy, will be considered to be a case of "clinical relapse". Any patient treated with single or multiple doses of Furazolidone in whom diarrhoea lasted as long as or more than the control placebo group will be considered as "therapeutic failure".

Patient will be termed bacteriologically positive if either direct plate or enrichment medium culture of stool as well rectal swab material grow V. cholerae. Patient will kept in the hospital for 7 days for daily cultures, or until both direct and enrichment cultures are negative for at least 3 consecutive days. If a patient becomes bacteriologically negative on both direct and enrichment cultures for at least two consecutive days and become subsequently positive then this will be considered to be

a "bacteriological relapse" case. On the 7th day of the study or after 3 consecutive days vibrio negative cultures, patients will be purged with 45 gm Magnesium sulphate in adults and/20 gm in children and their stool will be cultured to identify "carrier".

5. Data analysis:

Complete data sheets will be kept. Moreover "flow-sheet" will be made to enter the data 8 hourly. At the end of study, confirmed cases of cholera will be analysed. Means and standard diviations of measurements per kilogram body weight whenever applicable will be calculated. Comparison will be made by students "t" tests, Chisquare test and other appropriate statistical tests.

D. SIGNIFICANCE:

The optimum dose and duration of Furazolidone therapy in cholera remain yet to be known. The advantage of single dose therapy is that relatively small amount of drug will be required. Single dose schedule can be more reliably administered than the conventional multiple dose schedule. Even greater advantage of Furazolidone as a whole is that until now V. cholerae has not been found resistant invitro in Bangladesh. On the other hand MARV (Multiply antibiotic resistant vibrios) have been isolated in different parts of the world including Bangladesh (10). Patients may be abled to be discharged from hospital earlier after single dose treatment.

E. FACILITIES REQUIRED:

The Clinical Research Ward (Study Ward) and Microbiological laboratory facilities of ICDDR,B will be adequate for this study.

F. COLLABORATIVE ARRANGEMENTS:

This will be a collaborative study with NORWITCH EATON PHARMA OF U.S.A. The Pharmaceutical Company agreed to provide the drugs including placebo in indistinguishable form to make it a double blind, placebo controlled study.

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1. Lindenbaum J, Greenough WB, Isalm MR. Antibiotic therapy of cholera. Bull WHO 1967, 36, 871-883.

2. Carpenter CCJ, Barua D et al. Clinical studies in Asiatic cholera IV. Antibiotic therapy in cholera. Bull Johne Hopkins Hosp. 1966, 118, 216-229.

3. Islam MR and Ahmed SM. Single dose tetracycline therapy in cholera. Procedings of International Epidemiological Association. Regional meeting. Singapore 3-6 Oct. 1983.

4. Pickering LK, Dupont HL, Olarte J. Single dose Tetracycline therapy for Shigellosis in adults. JAMA 1978, 239, 853-854.

5. A comparison of a single dose and a five day course of Tetracycline therapy in bacilllary dysentery. J. Trop. Med. Hyg. 1969, 72, 170-72.

6. Pierce NF, Banwell JG, Mitra RC et al. Controlled comparison of Tetracycline and Furazolidone in cholera. BMJ. 1968, 277-80.

7. Chawdhury RN, Neogy KN, Sanyal SN, Gupta RK, Manji P. Furazolidone in treatment of cholera. Lancet 1968. Feb. 17, 232-33.

8. Karchmar AW, Curlin GT, Hoq MI, Hirschhorn N. Furazolidone in pediatric cholera. Bull Wld. Hlth Org. 1970, 43, 373-78.

9. Mazumder DNG, DeS, DeSP, Sircar BK. Minocycline, Tetracycline and Furazolidone in the treatment of cholera. Indian J. Med. Rɸs. 1977. Dec. 66 (6) 917-21.

10. Glass RI, Huq MI, Alim ARMA, Yunus M. Emergency of Multiple antibiotic resistant V. cholerae in Bangladesh. J. Infect. Dis. 1980, 142; 939-942.

SECTION III - BUDGET

Detailed Budget:

	Name	Position	% effort	Project Requirement Tk.	Dollar
1.	Personnel services:				
	Dr. M.R. Islam	Principal Investigator	50%	48000	-
	Dr. T. Butler	Co-investigator	5%	-	2000
	3 Senior Staff Nurses	-	25%	22500	
	1 Clerk	-	25%	4500	
	3 Cleaners	-	25%	9000	
2.	Supplies and Materials:				
	Stool culture 150 X 2 X 7 = 2100 specimens @ Tk. 25.00			52500	
3.	Equipments:				100
	1 calculator				
4.	Patients hospitalization 150 X 7 X 150			157,500	
5.	Outpatient - Nil				
6.	Transport - Nil				
7.	Travel (To present study outcomes in International Conferences)				6000
8.	Transport of things - Nil				
9.	Rent - Nil				
10.	Printing, Reporduction and Publication				500
		Total	Tk.	2,94,000	$ 8,600

BUDGET SUMMARY

	Taka	Dollar
1. Personnel	84,000	2000
2. Supplies	52,500	-
3. Equipments	-	100
4. Hospitalization	157,500	-
5. Outpatient	-	-
6. Transport	-	-
7. Travel	-	6000
8. Transportation of things	Nil	
9. Rent	Nil	
10. Printing & Publication	-	500
11. Contractual service	Nil	
12. Construction	Nil	
Total =	Tk. 2,94,000	US $ 8,600

Total incremental cost

= US $ 11,760 + 8,600 = 20,360

(US $ 1 = Tk. 25)

ABSTRACT SUMMARY

1. 75 adult male patients (over 15 years age) and 75 male children (below 8 years age) having history of less than 24 hours duration of illness with dark field positive for V. cholerae and without history of taking any drugs will be selected for the study. Patients with complications e.g. fever, pneumonia, convulsion or any other associated illness will be excluded from the study.

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

3. Though there is no known serious potential risk involved, every precaution will be taken to safeguard the interests of the patients. If necessary, study will be stopped in case of serious drug reactions observed in significant number of patients.

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 patient or their legal guardians. There is no procedure in the 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. 5 minutes will be enough to take such a clinical history.

7. The patient will get direct benifit through treatment of their illness.

8. The study will require no body fluids. Only rectal swab or stool will be taken for bacteriological cultures.

CONSENT FORM

SINGLE DOSE FURAZOLIDONE THERAPY IN CHOLERA

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

The ICDDR,B is carrying out research to find the most economic and effective way of treating cholera with antimicrobial agents in conjunction with intravenous and oral rehydration fluid. Furazolidone has been proved to be an effective drug against cholera. We like to compare the efficacy of a single dose Furazolidone with single dose Tetracycline or Placebo in adults and single dose Furazolidone with multiple doses Furazolidone or Placebo in children. If single dose Furazolidone is found to be as effective in cholera as other single or multiple doses of antimicrobial agents, then this will be the most economic therapeutic regimen. We would like to participate in this study for the benifit of mankind.

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

1. You will receive the best possible care during your stay in the hospital.
2. You will have to stay in the hospital for 7 days till the completion of study period.
3. During your stay, daily rectal swab and stool will be taken to see the period of vibrio excretion in the stool.

If you do not want to participate in the study, still you will be treated like other patients of this hospital. Moreover, if you wish, you can withdraw at any time from the study and still it will not hamper your care and treatment in any way.

Thus, understanding the above facts fully, if you are voluntarily willing yourself or allow your children to participate in this study, then please sign your name or give thumb impression below.

Signature of Investigator

Date: _____

Signature or Left thumb impression of patient or legal guardian.

Date: _____

Single dose Furazclidone in cholera

সম্মতি পত্র

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র স্বল্প ব্যয়ে ও কার্য্যকরী উপায়ে কলেরার চিকিৎসার জন্য খাওয়ার স্যালাইন ও শিরায় স্যালাইনের সাথে সাথে এন্টিবায়োটিকের দ্বারা চিকিৎসা উদ্ভাবনের জন্য গবেষণা চালিয়ে যাচ্ছে। ফিউরাযোলিডিন কলেরার চিকিৎসায় একটি কার্য্যকরী ঔষধ প্রমাণিত হয়েছে। আমরা এককমাত্রার ফিউরাযোলিডিনের সাথে বহুমাত্রার এবং এককমাত্রার ফিউরাযোলিডিনের সাথে এককমাত্রার টেট্রাসাইক্লিনের তুলনামূলক গবেষণা করব শিশু এবং প্রাপ্ত বয়স্কদের উপর আমরা এই উভয় দলেই একটি প্লাসেবো (ঔষধ সদৃশ কিন্তু কোন কার্য্যকমতা নাই) দিয়ে অন্যান্য মাত্রার সাথে তুলনামূলক গবেষণা করব। যদি এই গবেষণা থেকে দেখা যায় যে একক মাত্রার ফিউরাযোলিডিনের কার্য্যকমতা অন্যান্য মাত্রার ফিউরাযোলিডিনের কিংবা টেট্রাসাইক্লিনের একই রকম তাহ'লে এটা অনেক স্বল্প ব্যয়ে চিকিৎসার সহায়ক হবে। আমরা চাই যে, সমাজের উপকারের জন্য আপনি এই গবেষণায় অংশগ্রহণ করুন।

আপনি যদি স্বেচ্ছায় গবেষণায় অংশগ্রহনে রাজী থাকেন, তাহ'লে নিম্নলিখিত ব্যবস্থাদি নেওয়া হবে :-

১। হাসপাতালে থাকাকালীন অবস্থায় সম্ভাব্য সর্বোত্তম চিকিৎসার ব্যবস্থা করা হবে।

২। গবেষণা চলাকালীন সময়ে পুরো সাতদিন আপনাকে হাসপাতালে থাকতে হবে।

৩। হাসপাতালে থাকাকালীন অবস্থায়, প্রতিদিন পরীক্ষার জন্য রেকটাল সোয়াব ও মল নেওয়া হ'বে।

আপনি যদি গবেষণায় অংশগ্রহনে রাজী নাও থাকেন তবুও আপনাকে হাসপাতালের অন্যান্য রোগীর মত চিকিৎসা দেওয়া হবে। এছাড়াও আপনি চাইলে গবেষণা চলাকালীন সময়েও আপনি গবেষণা থেকে নিজেকে প্রত্যাহার করতে পারেন। এতে করে আপনার স্বাভাবিক চিকিৎসার কোন ত্রুটি হবে না।

অতএব, উপরের বক্তব্য সম্পূর্ণ বুঝে স্বেচ্ছায় যদি আপনি নিজে কিংবা আপনার শিশুকে গবেষণায় অংশগ্রহন করতে রাজী থাকেন তাহলে নীচে আপনার স্বাক্ষর কিংবা বৃদ্ধাংগুলের ছাপ দিন।

গবেষকের স্বাক্ষর

তারিখ----------

রোগীর বৃদ্ধাংগুলির ছাপ কিংবা স্বাক্ষর

তারিখ----------