(92

REVIEW BOARD ON THE USE OF [illegible]

CRL

Principal Investigator W.B. Greenough, III Trainee investigator(if any) _____

Application No 78-021 Supporting Agency(if Non-CRL) _____

Title of study Clinical Trial of Chlorproma-
ne (CPZ)as a therapeutic antisecretory
ent in cholera

Project status:
( ) New Study
( ) Continuation with change
( ) No change (do not fill out rest of

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

Source of Population:
a) All 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 possibly 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) N/A

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 of 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 N/A
Procedure for maintaining confidentiality N/A
Questionnaire or interview schedule N/A

* 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. Another indication as to when the questionnaire will be presented to the Board for review.

Agree to obtain approval of the Review Board on Use of Human Volunteers for any change involving the rights and welfare of subjects before making such change.

W.B. Greenough III

Principal Investigator

Trainee

Recd 21/8/78
78-021

DRAFT
May 2[illegible]

SECTION - 1 - RESEARCH PROTOCOL

1) Title: Clinical Trial of Chlorpromazine (CPZ) as a Therapeutic Anti-secretory Agent in Cholera

2) Principal Investigators: W. B. Greenough, III
CRL Clinical Research Physician
(to be named)
Jan Holmgren
I. Lonnroth

3) Starting Date: September 1978

4) Completing Date: December 1978

5) Total Direct Cost: $7,650

6) Abstract Summary: Reduction of fluid loss in cholera and E. coli (toxigenic) diarrhea may enable oral replacement therapy to succeed where it otherwise would fail. Chlorpromazine (CPZ), a drug used for many years in humans as a tranquilizer, has been shown to reduce fluid accumulation and adenylate cyclase activation in mice exposed to cholera toxin, E.coli enterotoxin (LT) and prostaglandin E_1 the dose used was 4 microgram, chlorpromazine intramuscularly per gram body weight. In humans this would be a total dose of 4 mg/kg body weight or 200 mgm in a 50 kg adult. This is well within dosage used routinely in treating acute anxiety states. A lower dose of 1mg/kg was also effective in mice. Human dosage would begin at the lower range to observe the effects. Cholera patients who were actively purging at rates above 100 ml/mg/24 hours would be admitted to a balance study where careful baseline measurements would be made followed by administration of CPZ. Each patient would serve as his own control. If a significant effect is present this should be clearly apparent in less than 10 well studied patients. If an effect is observed then studies of doses and route of administration would also be done.

7) Reviews:

a) Research Involving Human Subjects: _____

b) Research Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller/Administrator: _____

SECTION 11 - RESEARCH PLAN

A INTRODUCTION

1. Objectives:

a) To determine whether chlorpromazine will reduce fluid loss in cholera and non cholera watery diarrhea.

b) To establish threshold dose and optimal dose should objective(a) be true.

2. Background: Despite the successful applications of intravenous and oral rehydration in cholera (1) and the effective shortening of diarrhea by antibiotics (2), there are many patients who lose fluids so rapidly that without a high rate of intravenous therapy they go into shock and die. If a pharmalogic agent could be found which safely turned off intestinal secretion this would much simplify the treatment of cholera and diarrhea caused by enterotoxigenic E. coli. Even a partially effective antisecretory compound should be of considerable value, provided that it could reverse and not only interfere with the development of secretion. Thus, oral replacement therapy with sugar-electrolyte solutions, while being almost 100 percent effective in cases with mild or moderate dehydration, often fails in patients with very intense secretion (3, 5). An agent that could reduce secretion from e.g. 1,000 to 7000 ml per hour, i.e. 30%, might well make the difference between success and failure in the oral treatment of cholera (6).

ADENOSINE - 3' : 5' - cyclic monophosphoric acid (cAMP) regulates electrolyte and water transport across the small intestinal epithelium by stimulating secretion of anions from crypt cells as well as by inhibiting coupled sodium and chloride absorption by villus cells (7, 8). An increase in the intraepithelial level of cAMP may thus convert the small intestine into a net secretory state leading to diarrhea. This explains the severe dehydration conditions caused by vibrio cholera and certain Escherichia coli in which enterotoxins produced by the bacteria induce excessive secretion through activation of mucosal adenylate cyclase (9, 10,

In many other diseases, including some hormone-producing tumors, salmonellosis, shigellosis, coeliac sprue and diffuse regional enteritis, cyclic nucleotide regulated intestinal secretion may be at least partially responsible for the diarrhea (7, 8).

Reversal of Intestinal Secretion in Experimental animals by chlorpromazine

It should be possible to inhibit pathological intestinal secretion such as that in cholera by interfering with the production and/or handling of cAMP in the small intestine epithelium. It has been reported that the phenothiazine compound chlorpromazine (CPZ) inhibits hormonal stimulation of cAMP formation in several cell types (11, 13). CPZ was therefore, investigated as a potential inhibitor of intestinal secretion in mice. It was found that CPZ effectively inhibits the intestinal secretion in mice induced by cholera toxin, heat-labile E. coli enterotoxin, prostaglandin E_1, or dibutyryl -cAMP (14). Since all of these agents modulate intestinal electrolyte and water transport through increments in the intraepithelial level of cAMP it can be concluded that CPZ is a potent inhibitor of cAMP-mediated intestinal secretion irrespective of the stimulus for the rise in this nucleotide. The normal absorptive capacity of the small intestine on the other hand seems to be unaffected by CPZ. Thus, resorption of isotonic fluid from ligated small bowel segments occured at a similar rate in untreated mice and mice treated with a dose of CPZ, which completely prevented any fluid accumulation in response to the various diarrheogenic agents. CPZ inhibited intestinal secretion not only when administered prior to or simultaneously with the diarrheogenic agents but did also reverse secretion which was already established. This is evident from studies in which CPZ was injected 1 or 2 hours after the intestine had been challenged with cholera toxin, i.e. at times when the intestinal secretion rate is maximal. Under these conditions CPZ did not only inhibit the intestinal fluid accumulation markedly in comparison with that in untreated challenged animals as registered 6 hours after challenge, but also resulted in about 60-70 percent less fluid in the intestinal loops than was present in the moment CPZ was administered. This means that very significant net absorption took place in the CPZ-treated animals and thus supports that CPZ is capable of reversing the cholera secretory process more or less completely without disturbing intestinal fluid absorption (14).

4 ug CPZ per g body-weight was effective against any dose of cholera toxin; for inhibition of secretion after challenge with submaximal toxin amounts <1 ug CPZ/G was enough. Studies with radiolabelled CPZ revealed that the inhibition of intestinal secretion by CPZ was associated with a rapid incorporation of the drug into the membranes of both crypt and villus cells of the small intestine. The effective concentration range appears to be 0.1 - 1 ug incorporated CPZ per mg. membrane protein. Enzymatic analysis on intestinal mucosol membrane showed that cholera toxin stimulation of adenylate cyclase was totally inhibited in CPZ-treated animals; fluoride activation of the nezyme was inhibited too, while the basal adenylate cyclase activity was unchanged. However, also the mucosal membrane-associated protein kinase activity was strongly reduced. This might explain why CPZ inhibited the intestinal secretion induced not only by various adenylate cyclase activators but also by dibutyryl cAMP (14). The promising data in mice initiated experiments to test whether treatment with CPZ would also be effective in piglets with clinical, usually fatal diarrhea caused by enterotoxinogenic (ent$^+$)E. coli. The experimental design was to infect the piglets immediately after birth with a suspension of live ent$^+$ E. coli, and when watery diarrhea had been manifest for 2 hours administer CPZ in an im injection to half of the piglets leaving the others as controls. In three consecutive experiments comprising 30 piglets it has been shown that CPZ in 1, 2, or 5 mg. per kg body-weight very markedly totally turns off intestinal secretion concomitant with normalization of adenylate cyclase (14).

3. SPECIFIC AIMS:

To see whether chlorpromazine can [illegible] reduce intestinal fluid secretion in clinical cases with cholera and non-cholera watery diarrhea.

3. Rationale:

Chlorpromazine inhibits adenylate cyclase in mammalian cells. In experimental cholera and E.coli diarrhea it decreases fluid losses significantly. If this is true in human cholera then cases which currently can only be managed by intravenous therapy due to the extreme volumes lost might be able to be cured by oral rehydration alone in the presence of chlorpromazine.

This drug is inexpensive and can be taken by mouth and is widely used in medical practice for reasons other than diarrhea.

B. SPECIFIC AIMS:

To see whether chlorpromazine can turn off/reduce intestinal fluid secretion in clinical cases with cholera and non-cholera watery diarrhea.

C. METHODS OF PROCEDURE:

Patients who have been admitted to the treatment centre requiring intravenous rehydration will be selected based on rates of fluid loss in excess of 100 ml/kg/24 hours. Adult males only willqualify. Candidate patients admitted in shock with feeble or absent radial pulse will be selected. Tetracycline will not be given until after full hydration has been achieved and purging has begun.. Patients who then demonstrate a high rate of fluid loss will be admitted to the clinical research centre. All care excepting the administration of tetracycline will proceed on the basis of clinical indications and intake and output measurements. After an initial period of 8 hours chlorpromazine - 1mg/kg body-weight will be given intravenously. If there is no change in vital signs an additional 1mg/kg will be given one hour later. The following observations will be made:

1. Blood pressure, pulse and respiration every 1 hour.

2. Intake and output every 2 hours.

3. State of alertness will be assessed every hour with vital signs.

4. Blood will be drawn at admission, 8 hours, 24 hours and at discharge for specific gravity BUN creatinine, glucose and electrolytes.

5. Stool electrolytes will be measured at 8 hours, 12 hours and 24 hours.

6. Body weight daily.

Should purging be reduced after chlorpromazine and then increased after the effect has worn off additional doses of this drug may be given timed in such a way as to clearly demonstrate a reduction in rate of stool output over the control period levels. If no effect is observed at doses of 1 mg/kg and no adverse effects are seen the dose will be increased in succeeding patients up to a maximum of 4 mg/kg/24 hors.

During the study period although all hydration with the exception of water to drink will be intravenous. Patients will be allowed to eat a soft diet when hungry as is usual with cholera patients. Patients will be hospitalised only as long as diarrhea persits.

Risks to Subjects

The main risk associated with the use of chlorpromazine is transient orthostatic hypotension. Patients will be lying down and will have their blood pressure monitored very closely. The tranquilization effects should be beneficial to patients who are apprehensive about their severe illness and the unfamiliar procedures associated with their care. There will be no unusual measurements made and all treatment will be opimized due to the careful observation and measurements of hydration and intake and output.

D. SIGNIFICANCE:

Reduction of fluid losses by an inexpensive pharmacologic agent may markedly reduce the need of intravenous fluids in cholera. If successful early administration by the oral route could avert the need of any treatment except oral rehydration.

E. FACILITIES REQUIRED:

1. Two beds in the clinical research center study ward with nursing coverage sufficient to perform the measurements and physician attendance around the clock. The same physician may also be attneding other study patients.

2. Laboratory technicians stationed in the treatment centre for darkfield exam with one male and one female attendent to take rectal cathter specimen.

F. COLLABORATIVE ARRANGEMENTS:

This study will be done in collaboration with Drs. Jan Holmgren and I. Lonnroth of the University of Goteborg, Sweden.

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SECTION III - BUDGET

A. DETAILED BUDGET

1. PERSONNEL SERVICES

Name	Position	% of Effort or number of days	Annual Salary	Taka	Dollars
Dr. W.B. Greenough,III	Investigator	10	$ 50,780	---	5,078
Dr. Jan Holmgren	Investigator	10	No cost to CRL		
Dr. I. Lonnroth	Investigator	10	No cost to CRL		
	Res. Physician	25	Tk. 33,060	8,265	
				8,265	5,078

2. SUPPLIES AND MATERIALS

Those involved in patient care in clinical research centre study unit.

3. EQUIPMENT — None

4. PATIENT HOSPITALIZATION

	Unit Cost	Amount required
Number of patient days - 100	Tk.150.00	Tk. 15,000

5. OUTPATIENT CARE — None

6. CRL TRANSPORT

Mileage - Dacca — None

7. TRAVEL AND TRANSPORTATION OF PERSONS

Local Travel — None

International Travel

½ roundtrip ticket - Goteborg to Dacca for Dr. J. Holmgren $720

8. TRANSPORTATION OF THINGS None

9. RENT, COMMUNICATIONS & UTILITIES None

10. PRINTING AND REPRODUCTION $300

11. OTHER CONTRACTUAL SERVICES None

12. CONSTRUCTION, RENNOVATION, ALTERATIONS None

B. BUDGET SUMMARY

(Sept. '78 thru Dec. '78)

CATEGORY	Taka	Dollar-
1. Personnel	8,265	5,078
2. Supplies		
3. Equipment		
4. Hospitalization	15,000	
5. Outpatients		
6. CRL Transport		
7. Travel Persons		720
8. Transportation Things		
9. Rent/Communication		
10. Printing/Reproduction		300
11. Contractual Services		
12. Construction		
TOTAL	23,265	6,098

Total $ 7,650

Conversion Rate $1.00 = Tk. 15.00

Abstract Summary

A clinical trail will be done with 20 patients who are actively purging and V.cholerae positive to determine whether Chlorpromazine will decrease the rate of fluid loss in clinical cholera. Chlorpromazine has been shown to inhibit cholera toxin stimulated adenylate cyclase and reduce fluid loss in rats. Adult male patients will be admitted to the Clinical Research Unit of CRL, Dacca; where they will be thoroughly examined and continuously observed. Intravenous fluid replacement will be given to according to clinical indication and blood protein and electrolytes Careful intake and output measurements will be done. After baseline fluid loss has been established Chlorpromazine will be given intramuscularly 1mg/kg. Vital signs will be measured frequently and only fully hydrated patients will receive the drug. Observations of changes in output will be made.

1. Patients will receive best possible care of their cholera except antibiotics will not be given.

2. Informed consent will be obtained but no extraordinary steps will be taken to protect confidentiality of the medical records.

3. Chlorpromazine in the dose to be used is a safe drug that has been in long use. However, since orthostatic hypotension can occur patients will be kept lying down for at
le least two hours after receiving the drug and vital signs will be monitored. The rare idiosyncratic reactions of cholestatic jaundice and rashes will be explained.

4. There is a potential of real benefit to the patients we anticipate a decrease in fluid loss in response to treatment.

CONSENT FORM

CHLORPROMAZINE IN CHOLERA

The Cholera Research Hospital is using an injection which may reduce or stop your diarrhea. This medicine is widely used to calm anxiety. Since we do not know definitely that it will help you, special attention will be given to you during your treatment. This will include frequent measurements of how much fluids you are given and how much diarrhea you have. Blood tests to be sure you have a normal amount of salt and water in your body will be done.

If you do not want to have this medicine you will still be cared for. Should you join this study you may withdraw from it at any time and you will still be cared for.

_____ _____

Investigator's signature

_____ Date:

কলেরার ফ্লোরোমাজিন ওষুধের ব্যবহার
নিরীক্ষার জন্য

সম্মতি পত্র

কলেরা সাধারণ হাসপাতাল নদীয়া ইনভেস্টিগেশন
ওষুধের কার্যকারিতা আমার আপনার উপরিস্থিত প্রকোপ
কমাইতে অথবা বন্ধ করিতে পারে। উদ্বেগ
নিরীকরণার্থে এই ওষুধ ব্যাপকভাবে ব্যবহার করা
হইতেছে। যেহেতু এই ওষুধ আপনাকে আরোগ্য
করিতে পারিবে কিনা তাহা আমরা সঠিকভাবে
বলিতে পারিনা, সেহেতু আপনার চিকিৎসার
চলাকালীন সময়ে আপনার প্রতি ডিকোস বজ্র
দেওয়া হইবে। ইহাছাড়া, আপনাকে যতখানি
তরলীয় পদার্থ দেওয়া হইয়াছে তাহা প্রায়শঃ
পরিমাপ করা হইবে যেন আপনার ডায়রিয়ার
প্রকোপ কিরকম তাহাও লক্ষ্য করা হইবে।
আপনার করীষে রক্ত ও মিউকাসের
পরিমানের জন্য দিনে বার পরীক্ষার মাধ্যমে
উহা নিরিক্ষণ করা হইবে।

আপনি এই ওষুধ ব্যবহার করিতে অনিচ্ছুক
হইলেও আপনার রোগের চিকিৎসা করা
হইবে। এই সাধারণ হাসপাতাল ত্যাগ করিবার
পর যে কোন সময়ে আপনি আপনার সম্মতি
প্রত্যাহার করিতে চাহিলেও আপনার রোগের
সুচিকিৎসার বন্দোবস্ত করা হইবে এবং
আপনার উপযুক্ত যত্ন নেওয়া হইবে।

গবেষকের স্বাক্ষর

রোগীর