tachment 1. Date 12.12.79

REVIEW BOARD ON THE USE OF HUMAN SUBJECTS, ICDDR,B.

incipal Investigator Dr. T. Merishita & Dr. R. Islam

plication No. 80-002

tle of Study Bio-clinical studies in diarrhoeal diseases

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) Keio University, Japan.

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 Board:
___ 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 Board for review.

agree to obtain approval of the Review Board on the Use of Human Subjects for any changes volving the rights and welfare of subjects before making such change.

80-002
Rec'd 20/12/79

SECTION 1 - RESEARCH PROTOCOL

1. Title : Bio-clinical studies on diarrhoeal diseases.

2. Principal Investigator: Dr. Tetsuo Morishita
Dr. Rafiqul Islam
and Dr. P.K. Bardhan

3. Starting Date: January 1980

4. Completion Date: February 1980

5. Total Direct Cost: $ 5,596.5

6. Availability of Funds:
a) Scientific Director's Remarks:

b) Controller's Remarks:

7. Abstract Summary: Gastro-intestinal hormones such as VIP (Vaso-active intestinal polypeptide), GIP (gastric inhibitory polypeptide), glucagon, gastria, CCK-PZ (Cholecysto kinine-pencreazymin), substance-P, motilin and caerulein play important roles in the mechanism of production of intestinal secretion, motility associated with diarrhoea. This has been proved experimentally and clinically. The levels of cyclic AMP, cyclic GMP, gastrin, glucagon, insulin and secretin in the peripheral blood of cholera patients have been reported but not inother diarrhoeal agents of similar nature like E.coli and vibrio para haemolyticus etc. Plasma cyclic AMP levels is significantly higher in the acute stage than the convalescent stage. It is also reported that VIP, glucagon secretin and CCK-PZ increase the tissue level of

cyclic AMP. These hormones may induce excessive intestinal fluid secretion by increasing the activity of cyclic AMP in human cholera and other diarrhoeal diseases.

The objective of this study is to investigate the variations of the levels of these intestianl hormones in acute and convalescent phases of diarrhoea diseases in adults.

8. Review:

a) Research involving human subjects : _____

b) Research REview Committee : _____

c) Director : _____

d) BMRC : _____

e) Controller/General Manager, adm: _____

SECTION 11 - RESEARCH PLAN

A. Introduction:

1. Objective:

The objective of this type of collaborative study is for better understanding the role of the intestinal hormones in the mechanism of production of watery diarrhoea in cholera, E.coli and V.parahaemolyticus.

2. Background:

Biochemical studies on human cholera in 1974 at San Lazaro Hospital in Manila, clinical studies on variation of plasma cyclic AMP and several hormones and amines, serum diarrheagenic substances etc have revealed that plasma cyclic AMP level was extremely higher in the acute stage compared with the convalescent stage. It was also reported that VIP, glucagon, secretin and CCK-PZ increase the tissue level of cyclic AMP so these hormones may likely induce excessive production of in-intestinal fluid by increasing the activity of cyclic AMP in human cholera and other diarrheal disease. (For detailed background see references).

3. Rationale:

Many investigators have shown experimentally that gastro-intestinal hormones such as VIP, GIP, glucagon, gastrin and secretin induce intestinal secretion and substance-P, gastrin CCK-PZ, motitin and caerulein cause contraction of small intestinal tract. Clinically in relation to tumor associated diarrhoea, gastrin in Zollinger-Ellison syndrome and VIP glucagon, secretion in WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome are suggested to be responsible for watery diarrhea. Some experimental evidences show that VIP, glucagon, secretin and CCK-PZ increase tissue cyclic AMP. So there may be some significant relationship of these substances present in the mechanism of production of diarrhea in cholera and allied illnesses.

B. Specific Aims:

To observe:

1. The difference of the levels of peripheral cyclic AMP, VIP, glucagon and substance -P among cholera, E.coli, and V. parahaemolyticus infections in acute convalescent and subsequent follow up stages.

2. The variations of levels of these substances in different types of diarrheal illness.

3. The relationship between cyclic AMP and gastrointestinal hormones.

4. The relationship between these substances and clinical symptoms, signs, other laboratory findings etc.

C. Methods and Procedures:

1. Case selection - only adult patients will be selected for study. Severly dehydrated case with short onset and having not received any antibiotics before admission will be admitted in the study ward. About 15 cases from each group of cholera, E.coli, and V.paraheamolyticus will be studied.

2. 5 ml of venous blood will be drawn in addition to usual electrolyte blood from each patient on admission, 24 hours after admission, on discharge and about 2 weeks after dischage.

3. The plasma and serum are separated without delay and stored at -20° C.

4. The plasma and serum will be transported by airplane refrigerated for radioimmunoassay in Tokyo.

5. Regular clinical information of the patients like clinical history, vital signs, intake and outputs etc will be recorded as usual.

6. Patients will be treated only with intravenous fluid alone.

7. No antibiotics will be given.

8. There will be no restriction of diet.

D. Significance:

1. It is expected that antagonists to the substances which increases the production of cyclic AMP may inhibit the production of diarrhea.

2. The mechanism, systemic influence and pathophysiological condition in cholera and allied diarrheal disease may be understood in a better way.

F. Facilities required:

1. Present study ward, physicians and nursing staff can be utilized for patient's care and sample collection etc.

2. Field staffs from the existing community studies can be used for follow up samples.

3. Centrifuze, freezer (below -20° C), syringes, needles etc are available in ICDDR,B.

4. CRL transport will be required to bring back patients by the field staff for follow up samples.

5. Bacteriological support as well as animal resources for ST, LT study will be required.

F. Collaborative Arrangements:

This will be collaborative study between ICDDR,B and School of Medicine, Keio University, Tokyo, Japan.

The samples will be transported for redioimmunoassay in Tokyo.

REFERENCES

1. Bloom SR, et al : VIP and a watery diarrhoea syndrome. Lancet 1: 14, 1973.

2. Morishita T, et al: Clinical studies on cholera. Part 11, Variation of Blood cAMP and several hormones in the course of cholera. Proce. on 11th Jt. Conf. on Cholera - US -Japan Cooperative Med. Sc. Progr. 84 , 1975.

3. Morishita T, et al: Clinical studies on cholera- variation of blood hormones and amines in course of cholera. Proc. 12th Jt. Conf. on Cholera - US - Japan Coop. Med. Sc. Program. 1976.

4. Schwartz CJ, et al: VIP stimulation of adenylate cyclase and active electrolyte secretion in intestinal mucosa. J. Clin. Inv. 54: 536, 1974.

5. Barbezat and Grossman: Intestinal secretion stimulatin by peptides. Science (Washington DC) 174: 422, 1971

6. Hibi F, et al: Serum diarrhoeagenic substances in human cholera. 13th Jt. Conf. on Cholera. US - Japan Coop. Med. Sci. Prog. 1977.

7. Polak JM, et al: Cellular localisation of GIP, GUT 14: 284, 1973.

8. Polak JM, et al : Cellular localisation of VIP, GUT 15: 720, 1974.

9. Said SI, et al: Elevated plasma and tissue levels of vaso-active intestinal polypeptides in the watery diarrhea syndrome. N. Eng. J. Med. 293: 155, 1975.

10. William Y. Chey, et al: The endocrine control of gastro-intestina- functinn. Advances in Internal Medicine . Vol: 23, 1978, p - 61.

SECTION 111 - BUDGET

A - DETAILED BUDGET

1. Personnel Services:

Name	position	%of time used	Salary Tk.	$
Dr. Tetsue Morishita	scientist Keio Univ. Japan	100%	salary will be paid by keio Univ.	
Dr. R. Islam	Chief Phys and Assc. Scntist.	50%	7,000	
Dr. P.K. Bardhan	Physician	50%	3,000	
5 study nurse	senior staff nurse	50%	10,000	
Veterinarian	-	5%	500	
2. Field assistants	F.A.	100%	3,000	
Microbiology Techn.	Res. Techn.	50%	1,500	
			25,000	

2. Supplies and Materials:

Item	Unit cost	Taka	Dollar
Culture of stool	50X15.5	775	-
ST, LT	50X3	150	-
Mice	50X3	150	-
Stationary, forms, paeprs and pencils etc.	-	500	

Small plastic tubes for transportation of serum and plasma from Dacca to Tokyo will be brought from Japan by Dr. Morishita. No cost to ICDDR,B

Total Tk.1575.

3. Equipments: None

4. Patients hospitalization

No. of hosp. days	unit cost	amount required
150 days	Tk. 150	22,500

5. Out patient care: None

6. CRL Transport

Dacca	1X50X200	Tk. 10,000
Other charges for boats, bus, rickshaws etc		Tk. 1,000
		tk. 11,000

7. Travel and Transportation of Persons:

Local Travel Nil

International Travel:

Transport (air) - Round trip ticket from Tokyo to Dacca for Dr. Morishita will be borne by Keio Univ.

8. Transportation of things:

will be borne by the Keio Univ., Japan.

9. Rent,Communication and Utilities:None

10. Printing and Reproduction $300

11. Other contractual services None

12. Construction, Rennovation, Alterations:

None

B - BUDGET SUMMARY

	Category	Taka	Dollar
1.	Personnel	25,000	
2.	Supplies	1,575	
3.	Equipment	Nil	
4.	Hospitalization	22,500	
5.	Outpatient	Nil	
6.	ICDDR,B Transport	11,000	
7.	Travel persons	Nil	
8.	Transportation of things	Nil	
9.	REnt/Communication	Nil	
10.	Printing & Reproduction		300
11.	Other contractual service	Nil	
12.	Construction/Rennovation	Nil	
	TOTAL TK.	60,075	$ 300
	30% overhead	18,022	90
	GRAND TOTAL	78,097	390

*=$5,596.5
conversion rate $1=Tk.15/

ABSTRACT SUMMARY

In collaboration with School of Medicine, Keio University, Tokyo, Japan; a bio-clinical study will be done in ICDDR,B Study ward with 50 adult patients who are actively purging due to V.cholerae, E.coli, or V.parahaemolyticus, in acute, convalescent and 2 weeks after discharge for better understanding the role of the intestinal hormones and amines like VIP, GIP, glucagon, gastrin, CCK-PZ, Substance-P, motilin and caerulin etc in the mechanism of production of intestinal secretion, motility etc in watery diarrhoea. The level of cyclic AMP, cyclic GMP, gastrin, glucagon, insulin and secretin in the peripheral blood of cholera patients have been reported but not in other diarrhoeal agents of similar nature. VIP, glucagon, secretin and CCK-PZ increase the tissue level of cyclic AMP. These hormones may be responsible for excessive intestinal fluid secretion by increasing the activity of cyclic AMP in human cholera, E.coli and other diarrhoeal diseases. Study design is planned to measure the variations of intestinal hormones in acute, convalescent and 2 weeks after full recovery.

Initial fluid replacement and subsequent maintenance will be done with cholera saline alone. Careful intake and output measurement, vital signs, etc will be done. 5 ml of venous blood will be drawn on admission, 24 hours after admission, on discharge and about 2 weeks after discharge. After quick separation of plasma and serum and stored at -20°C and subsequently will be sent to Tokyo for radioimmunoassay.

1. Patient will receive best possible care of their diarrhoea

2. Informal concent will be obtained for extra blood drawing.

CONSENT FORM

The ICDDR,B is an organisation devoted to diarrhoeal illnesses. In the present study, we want to investigate the variation of the level of cyclic AMP, VIP, glucagon, and substance-P of the venous blood in cholera, E.coli, and V.parahaemolyticus. These are gastriintestinal hormones which play important roles in the mechanism of production of watery diarrhoea. You will receive special attention during your treatment. Only 5 ml of your venous blood will be necessary in each time on admission, 24 hours after admission, on discharge, and 2 weeks after discharge from the hospital. You will be provided transport to send you home after recovery and 2 weeks after your discharge to bring you back.

You have the right to refuse to participate or even withdraw anytime from the study and still you will be cared for .

_____

Invesitgator's signature

_____

Patients' signature or thumb impression

Date : _____

সম্মতি পত্র

বাংলাদেশ আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র নানাবিধ উদরাময় রোগের চিকিৎসা ও গবেষণায় নিয়োজিত । কলেরা, ই,কলাই এবং শিগেলা প্যারাহিমোলাইটিকস প্রভৃতি জীবাণু দ্বারা সৃষ্ট উদরাময় রোগে রোগীদের শিরায় রক্তে সাইক্লিক এ এম পি, জি আই পি, গ্লুকোগন এবং পি-সাবস্টেন্স নামক কতকগুলো জৈবিক পদার্থের পরিমানের তারতম্যের পরিমাপ করতে চাই ।

পাকস্থলী ও অন্ত্রের এই হরমোনগুলোর ক্রিয়ার ফলেই পানির মত পাতলা পায়খানা হয় । চিকিৎসাধীন থাকাকালে আপনার বিশেষ যত্ন নেওয়া হবে । শুধু মাত্র ভর্তির সময়ে, ভর্তির চব্বিশ ঘন্টা পরে, হাসপাতাল থেকে ছুটির সময়ে এবং ছুটির দু'সপ্তাহ পরে প্রতিবারে আপনার শিরা থেকে পরীক্ষার জন্য পাঁচ সি সি করে রক্ত নেওয়া হবে । হাসপাতাল থেকে ছুটির পরে বাড়ী যাবার এবং দু'সপ্তাহ পরে হাসপাতালে আসার জন্য যাতায়ত ব্যবস্থা যথা সম্ভব আমরাই করব ।

গবেষণায় অংশগ্রহণ করতে আপনার আপত্তি থাকলে অথবা গবেষণা চলাকালে কোন সময়ে আপনার উপরে গবেষণা বন্ধ করে দিতে চাইলে আপনি তা পারবেন । তবু আপনার চিকিৎসা যথারীতি চলতে থাকবে ।

চিকিৎসকের স্বাক্ষর

রোগীর স্বাক্ষর অথবা
বৃদ্ধাংগুলির ছাপ

তারিখ----------