Attachment 1. 206

Date 1 May 86

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. M. Shahrier

Application No. 86-016 Dr. G.H. Rabbani

Title of Study "Double blind controlled trial of berberine sulphate in treating childhood diarrhoea"

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) UNDP

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:

NA

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.

(PTO)

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

Mamun Shahrier
Principal Investigator

Trainee

4/5/86

86-016
1.5.86

SECTION 1 - RESEARCH PROTOCOL

1.	**TITLE:**	DOUBLE BLIND CONTROLLED TRIAL OF BERBERINE SULPHATE IN TREATING CHILDHOOD DIARRHOEA (A Collaborative Study of ICDDR,B and Dhaka Shishu Hospital).
2.	**PRINCIPAL INVESTIGATOR FROM ICDDR,B:**	Dr. Mamun Shahrier and Dr. G.H. Rabbani
	PRINCIPAL INVESTIGATOR FROM DHAKA SHISHU HOSPITAL:	Prof. M.S. Akbar, MRCP
	CO-INVESTIGATORS:	Dr. Nurul Amin, Dr. Naila Khan.
3.	**STARTING DATE:**	April 1986
4.	**COMPLETION DATE:**	December 1987
5.	**TOTAL DIRECT COST:**	US $21,466 (supported by UNDP).
6.	**SCIENTIFIC PROGRAMME:**	This protocol has been approved by the Pathogenesis and Therapy Working Group.

(Prof. Roger Eeckels)
Acting Associate Director, PTWG

Date: 17/2/86

7. ABSTRACT SUMMARY:

Berberine sulphate, a plant alkaloid has long been used as a traditional antidiarrhoeal medication in India and China. The drug inhibits toxin-induced diarrhoea in animals and is marketed in India and Japan. Recently, we have reported from ICDDR,B that a single-dose of 400 mg of berberine reduces the fluid-loss by 30%-50% in adult subjects with diarrhoea due to Vibrio cholerae and enterotoxigenic Escherichia coli. This encouraging result in adults together with the reported safety and efficacy of berberine in children (Gupte, 1975) stimulate us to evaluate its therapeutic usefulness as an anti-diarrhoeal agent in children. We are proposing a double-blind, randomized, controlled trial in 200 diarrhoeal children aged 1-10 years who will be studied at ICDDR,B and Dhaka Shishu Hospital in a collaborative research programme. All children with watery diarrrhoea will have their stool screened for V. cholerae by dark field microscopy. After initial clinical assessment, rehydration and quantification of purging for 4-hr, children will be randomly assigned to a treatment and a placebo group. Berberine will be given orally at a dose of 10 mg/kg per day for 3 days. Intake of intravenous fluid, oral rehydration fluid and plain water, and output of stool, urine and vomit will be measured until diarrhoea is stopped. Any unpleasant effect will be recorded. Stool will be cultured for bacteriologic diagnosis. Children will be released from the hospital after recovery of the diarrhoeal illness. Clinical features including body weight, intake and output of fluids will be compared between the treatment and control group to assess the effect of the drug. This study is an attempt to identify a low-cost, simple and effective antidiarrhoeal drug.

8. REVIEWS:

(a) Ethical Review Committee: ----------

(b) Research Review Committee: ----------

(c) Director, ICDDR,B: ----------

SECTION II : RESEARCH PLAN

A. INTRODUCTION

1. Objectives

To investigate the clinical usefulness of berberine sulphate as an antidiarrhoeal agent in treating children with cholera and non-cholera watery diarrhoea.

2. Background

Recent reports from ICDDR,B indicate that berberine is clinically useful in treating adult patients with cholera (Butler 1984) and enterotoxigenic Escherichia coli diarrhoea (Rabbani 1985). This antisecretory effect in adult patients together with its previously reported antidiarrhoeal and antimicrobial activity in experimental system, encourages us to evaluate the therapeutic efficacy and safety of berberine in treating children with diarrhoea due to Vibrio cholerae and enterotoxigenic E. coli.

The plant alkaloid berberine (Fig. 1) derived from the root and bark of Berberis aristata, a spiny, deciduous shrub with yellow flowers (burbery bush), extracts of which have been used as antidiarrhoeal medication in the practice of Ayurvedic medicine in India and in the traditional medicine of China for the past 3,000 years (Sack 1962). As one of the several indigenous antidiarrhoeal plant extracts being studied in India by Dutta et al. approximately 25 years ago, it alone was found to significantly reduce the severity of Vibrio cholerae infection in the infant rabbit model (Dutta 1962). Since then, the drug has been investigated widely by Indian scientists and has been found to have activity against a broad array of infections agents such as selected bacteria including V. cholerae (Dutta 1962), protozoa (Amin 1967), fungi (Subaiah 1969),

and leishmania (Munshi 1972).

Furthermore, it has been used with reported success to treat a number of specific acute diarrhoeal diseases including cholera (Lahiri 1967) and giardiasis (Gupte 1975) and is pharmaceutically marketed in India. However, there are no published report of a well-controlled therapeutic trial of berberine in children with diarrhoea caused by specific enteric bacteria such as V. cholerae or E. coli. It has been traditionally used as a tonic, astringent, diaphoretic, antipyretic and purgative, in cases of splenomegally and jaundice, in remittent and intermitent fevers, in neuralgia, in billous complaints and diarrhoea. Mixed with honey it is applied externally to aphthous sores, abrassions and ulcerations of the skin (Said et al 1969).

Berberine (mol. wt. 384.4) is mentioned as a "bitter" in the British Pharmaceutical Codex, 1969 and also in the Pharmacopoeia of Japan, 1976. It is an acid sulphate (5,6 - Dihydro - 9,10 dimethoxybenzo [9] - 1,3 - benzodioxolo [5,6-] quinolizinium hydrogen sulphate [$C_{20}H_{18}NO_4HSO_4$]. The Extra Pharmacopoeia (Martindale 1982) lists berberine as an acid salt, a quaternary alkaloid present in hydrastis. Its uses mentioned in pharmacopoeia include treatment of cholera and enteritis, cutaneous leishmaniasis, amoebiasis and trachoma. Listed adverse effects are respiratory depression and circulatory collapse in large doses.

The pioneer study of berberine in experimental cholera was Dutta and Panse's 1962 work. They used infant rabbits and found that among several indigenous plant extracts tested, only berberine prevented diarrhoea and death when given both before and 8 h after infection. The authors did not, however, find berberine to be vibriocidal.

Subbaiah and Amin in 1967 found berberine sulphate useful in the prevention of experimental Entamoeba histolytica infection in 3-4 week old golden hamsters, and well tolerated by the animals upto a dose of 100 mg/kg. Amin, Subbaiah, and Abbasi assessed the antimicrobial activity of berberine sulphate in 1969, and found that it was more potent than chloramphenicol and tetracycline against V. cholerae and was also bactericidal against this organism. Datta, however, found that berberine was less active than tetracycline and chloramphenicol and Nair, Modak, and Venkatraman (1967) found it to be vibriostatic rather than vibriocidal.

In clinical trials in 1967 berberine was shown to be more effective than chloramphenicol in the treatment of cholera and nonspecific diarrhoea (Lahiri, 1967). Further clinical studies in India in the late 1960's and early 1970's confirmed the drug's clinical efficacy in diarrhoeal disorders - these include studies by Kamath (1967), Deshpande (1969), Sharda (1970), Sharma et al. (1970), and Desai et al. (1971). In 1975, Gupte showed that berberine was both effective and well tolerated at a dose of 10 mg/kg per day in the treatment of giardiasis with efficacy somewhat less than that of standard therapies.

Raswat, a traditional crude dried preparation of Berberis aristata, was also effective against cholera toxin-induced diarrhoea at a dose of 1-2 mg/kg (Said, 1969).

Earlier, Dutta and co-workers (1972) had shown that oral administration of berberine to infant rabbits 18-24 hours before the intra-intestinal administration of cholera toxin prevented the development of diarrhoea or significantly prolonged survival time, whereas berberine given later was ineffective. They related this result to the finding by Bhide et al (1969) that the concentration of berberine in the blood of infant rabbits reaches a maximum 8 hours after small intestinal administration (by intubation) with some of the drug still detectable after 72 hours. Mekawi (1968) showed that 0.3 mg of berberine injected I.M. protected mice from death from cholera infection, and also showed that the drug protected them against cholera toxin.

Further studies by Akhter and co-workers (1979) showed that berberine given orally significantly prolonged the latent period and reduced the frequency and severity of diarrhoea in dogs provoked by Ipomoea turpethum root, a potent traditional purgative preparation. Berberine did not prevent diarrhoea caused by magnesium sulphate or castor oil. At a dose of 10 mg/kg it reduced intestinal morility in mice, and was more effective when given intra-peritoneally than when given orally.

Recent experimental work has confirmed the efficacy of berberine as an anti-secretory agent. Swabb and co-workers tested the effects of luminal berberine in the cannulated, perfused rat ileum using 14^{C} polyethylene glycol as a nonabsorbable marker. They found that berberine reduced cholera-toxin induced secretion of water, Na, Cl, and HCO_3 in a

concentration-dependant manner but did not alter normal ileal water and electrolyte transport. The effect of berberine on toxin-induced secretion became evident 60-80 minutes after exposure and was reversed 60-80 minutes after removal of berberine from the perfusate. Berberine also prevented the development of cholera toxin-induced villous tip oedema (Swabb 1981). Sack and Frochlich (1982) found that berberine sulphate inhibited by approximately 20% the secretory response to the heat-labile enterotoxins of V. cholerae and E. coli in ligated intestinal loop of rabbit.

The drug was effective when given both before and four hours after toxin administration, and by both intraluminal and parenteral administration. It did not inhibit the stimulation of adenylate cyclase by cholera enterotoxin and caused no histological damage to intestinal mucosa. Berberine also inhibited secretion due to the E. coli heat-stable enterotoxin in the infant mouse (Swabb 1981; Sack 1980).

In three separate controlled clinical trials at ICDDR,B 165 adult patients with diarrhoea due to V. cholerae and enterotoxigenic E. coli (ETEC) were treated with a single dose of 400 mg berberine given by mouth. All patients received intravenous acetate-electrolyte solution for rehydration but no antibiotics were given. There was a significant ($p < 0.05$) reduction of stool output of 40%-50% in both types of diarrhoea within 24 hours of starting berberine treatment (Butler 1984, Rabbani 1985). The antisecretory effect was more stronger in patients with ETEC diarrhoea than that in cholera. There were no major side-effects in these well hydrated diarrhoeal patients.

Pharmacology and safety of berberine

The study of berberine pharmakokinetics in humans is now possible, thanks to the development of sensitive and specific assay methods for detecting the drug in biological fluids (i.e. urine) (Miyozaki 1978a, Miyozaki 1978b). Pharmacology of berberine has been studied in detail by several workers (Sabir 1978, Sabir and Bhide 1971, Chopra 1932, Fukuda 1970, Mardika 1972, Shanbhag 1970, Vad 1971). Sabir et al. (1971) reported that berberine produced reversible and dose dependant hypotension in dog, cat and frog. It induces hypotension by directly acting on blood vessels. In mice, it lowers rectal temperature, reduces motor activity and reduces gut motility by anticholinisterase action.

The LD_{50} of berberine sulphate in mice was 24.5 mg/kg when given by intraperitoneal route (Sabir 1971); this is in close agreement with that of berberine bisulphate (27.5 mg/kg) found by Uchizumi (1958). In dogs,intravenous doses up to 45 mg/kg did not produce any lethal or gross toxic effect and the animals appeared normal for several days after injection (Sabir 1971). The mouse therefore appears to be more sensitive than dog to berberine. Berberine also inhibits the movement of isolated rabbit intestine and inhibited prostaglandin induced intestinal motility (Sabir et al. 1978). In human, berberine is poorly absorbed from the gut and is excreted in the urine (Miyozaki 1978a, 1978b).

Clinical safety of berberine has been established by human studies in India. The published reports of various workers suggest that berberine is safe in human though there is no definitive knowledge of its possible side effects. Sharda (1970) in his trial used berberine

to treat diarrhoeal children of age 2 months to 6 years at a dose of 25 mg 4 times daily in children up to 6 months and 50 mg first dose and 25 mg 4 times daily in children above 6 months. The total duration of treatment was up to 5 days. Vomiting was the only side-effect which occurred in 3 out of 50 cases. Sharma (1970) administered berberine to 65 children of age group 1 year to 5 years with acute diarrhoea at a dose of 25 mg 4 times daily up to 3 days with successful results and he did not observe any significant side-effects. Desai (1971) used berberine in 35 children, mostly below 3 years of age at a dose of 50 mg on admission and 25 mg 4 times daily for 5 days. The drug was well-tolerated and no significant side-effects were noted. Gupte (1976) used berberine at a dosage of 10 mg/kg in the treatment of giardiasis in 137 Indian children aged 5 months to 14 years for 10 days. He did not observe any significant side-effects during the treatment. From above mentioned studies we can anticipate that the chance of any significant side-effect is much less likely as the duration and dosage of berberine of our study will be less than most of the previous studies.

In summary, berberine has been shown to be an effective antisecretory agent in cholera and other diarrhoea syndromes by a great deal of experimental work in various animal models. Some evaluation in humans was also carried out with encouraging results, but there has been no published study of a trial in children with specific bacterial diarrhoea.

3. Rationale

The fundamental rationale of this study is to develop an effective, simple, low-cost and acceptable form of antidiarrhoeal therapy for children.

This study will provide an opportunity to evaluate the efficacy of a traditional medicine. Now the emergence of antibiotic resistance in micro-organisms is becoming alarming, specially that of V. cholerae to tetracycline (Glass 1982, Mahlu 1980), this study might help to develop an antidiarrhoeal agent to which resistance is unlikely and has never been reported. Our expected findings would thus provide a rational basis for the reported clinical efficacy of a traditional medication for the treatment of infectious diarrhoeal diseases.

B. SPECIFIC AIMS

1. To determine the antisecretory effect of berberine by measuring stool volume in berberine-treated diarrhoeal children as compared to untreated controls.
2. To determine the clinical safety of berberine in children with secretory diarrhoea.

C. METHODS AND PROCEDURES

Study population

The study will be carried out in collaboration with Dhaka Shishu Hospital. In total 200 children will be studied by selecting 100 from each hospital. This will be a double-blind, parallel, and controlled clinical study. The study will be carried out in children with cholera and non-cholera watery diarrhoea. Patients will be selected from ICDDR,B and Dhaka Shishu Hospital according to following characteristics.

Inclusion criteria

(1) Both boys and girls will be studied.

(2) Age of the child will be between 1 year and 15 years.

(3) History of onset of acute watery diarrhoea within last 24 hours.

(4) No previous treatment with antibiotics or antidiarrhoeal drugs.

(5) Stool may be either positive or negative for V. cholerae by dark field microscopy.

(6) For children with cholera, baseline purging rate of 20 ml per kg body weight over a period of 4 hours before allocation to treatment.

(7) For children with non-cholera diarrhoea, the baseline purging rate is 10 ml per kg over 4 hours.

(8) Voluntary agreement after informed consent by the guardians.

Random allocation of children to treatment and placebo group

After admission to the study ward, children who satisfy the above mentioned criteria will be randomly assigned to either (a) treatment group or (b) placebo-group using a permutted block design of fixed block length (Gore 1982). This method will ensure assignment of equal number of children in each group.

Drug administration

After diarrhoea has been manifested for four hours at a defined rate (see #6. # 7 above), children will be assigned to either treatment "A" (berberine) or to treatment "B" (placebo) according to the following schedule:

Children with cholera: (a) Treatment group : berberine 10 mg/kg per day in 3 divided doses for 3 days (50 children).

(b) Control group: Placebo preparation (50 children).

Children with ETEC diarrhoea: (a) Treatment group - berberine, 10 mg/kg per day in 3 divided doses for 3 days (50 children).
(b) Control group - placebo preparation (50 children).

Berberine sulphate and placebo: The active drug containing berberine and placebo will be supplied by the manufacturer, Allembic Chemical Works Company Ltd., Baroda 390003, India, without cost.

Exclusion criteria

Will be excluded from the study, patients who:

(1) are not able to comply with the study procedures as outlined in the protocol;
(2) are not expected to maintain oral medication due to vomiting;
(3) have any other concurrent medical condition that might interfere with the evaluation of the study medications;
(4) have clinical evidence of severe malnutrition.

Exclusion criteria during the course of study

Subjects who acquire any of the following conditions during the course of the study will be excluded from further participation:

(1) any adverse reaction warranting discontinuation of the study medications;
(2) any intercurrent illness or condition that might interfere with the evaluation procedures in this study (drop out).

In these instances, appropriate treatment will be given by the investigators.

Drop out accounting

Subjects who do not complete the study will be replaced according to the guidelines in this protocol. This will be done in order to preserve the

the study population as close as possible to 200 completed subjects.

Monitoring and treatment

Children will receive intravenous, electrolyte-acetate solution for initial rehydration and then oral rehydration solution to match their further stool losses. The later will be quantitated by 8 hours periods as long as each child has significant diarrhoea. Stool will be collected by using diaper bag in young children. It is difficult to separately collect urine from very young girls but we do not expect that this will significantly affect the results because of random allocation of all children in 1:1 basis between treatment and placebo group. Cesation of diarrhoea will be defined as having no liquid stool within the last 24 hours. Stool or rectal swab cultures will be done on admission to isolate V. cholerae and E. coli. Colonies that are typical of E. coli will be picked and kept preserved, until they are tested for toxin production using standard procedures. Each child's vital signs including blood pressure and level of consciousness will be recorded every 8 hours and any significant changes in physical condition will be noted.

Concomitant medications

Medications which are considered necessary for the child's welfare and which will not interfere with the study drug or its evaluation may be given at the discretion of the investigators. Administration of all such concomitant medications will be recorded on the appropriate page of the case report.

D. SIGNIFICANCE

The significance of the study is to develop a safe, effective and low-cost treatment of dehydrating diarrhoea.

Statistical methods

Trial size calculation: The sample size (n=200) for this trial is calculated assuming a 1:1 randomization between the treatment and placebo group using a permuted block design. We also assume to detect a 20% difference of stool output between the treatment and control group at 5% significance level with 90% statistical power.

Data analysis: Patients in the treatment and control groups will be compared with regard to their baseline purging rate, purging rate after treatment, and duration of diarrhoea. Each patient's baseline purging rate will be compared with his rate after treatment.
According to our previous observation, the stool output of cholera patients tend to follow a non-normal distribution with large variance, particularly when the sample size is small. The nature of the distribution of stool data of the present study will be examined by statistical tests of normality and skewness. Depending on the nature of distribution, either parametric or non-parametric tests will be used to examine the difference between the two groups. Alternatively logarithmic transformation of the stool data may be applied to stabilise the variance.

E. FACILITIES REQUIRED

1. Office space	:	Present office space will be used.
2. Laboratory space	:	The present laboratory will be utilised.
3. Hospital resources	:	200 children will be studied.
4. Animal resources	:	Suckling mice will be utilized for toxin assay.
5. Logistic support	:	None.
6. Major equipment	:	Weighing scales. (one).
7. Others	:	None.
8. Transport	:	None.

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ABSTRACT SUMMARY (for Research Review Committee)

Controlled trial of berberine as an antisecretory agent in cholera and ETEC diarrhoea in children.

1. This study will be conducted in 200 children with cholera and ETEC diarrhoea with purging. We will test berberine sulphate which has been shown to be an effective antisecretory agent in V. cholerae and E. coli toxin-induced diarrhoeas in a number of animal experiments and in human trials. Berberine is produced and marketed in India and Japan and is believed safe for human use; it has been found to be essentially free of side effects at a dose of 10 mg/kg per day in children of age 2 months to 5 years.

2. The patients will be randomly assigned to treatment and control groups. They will be observed for 4 hours to determine their baseline purging rate. Those assigned to the treatment group will then be given a dose of berberine equal to 10 mg/kg body weight for 3 days. Stool volume will thereafter be measured during 8 hour periods until diarrhoea stops. Childrens will be rehydrated by the intravenous route initially and then with oral rehydration solution. The study should not subject either treatment or placebo group children to any significant risks. It is not expected that serious side effects of berberine administration will be found.

3. Not acceptable.

4. Patient confidentiality will be maintained. All data will be abbreviated and will be published without reference to the subject's name and identity.

5. Informed consent will be obtained from each child's guardian.

6. No personal interview is required.

7. Benefits to the sick child involved in the study will be the cost-free treatment of diarrhoeal illness. General benefits to society include the possible identification of a valuable antisecretory drug for cholera and non-cholera diarrhoea.

8. No retrospective hospital records will be used. No biological specimens except stool will be taken from the subjects.

ICDDRB BUDGET PROPOSAL--1986
Program Name: PTWG
Project/Protocol/Branch: BERBERINE IN CHILDREN
Principle Investigator: M SHAHRIER
Budget Code: 02MSBERB
Protocol No:

SUMMARY BUDGET

3100 Local Sal	2790
3200 Intl Sal	0
3300 Consultants	0
3500 Travel Local	0
3600 Travel Intn	0
3700 Supplies	5200
3800 Other costs	720
4800 Inter Dept'l	12756
Total Direct Operating	21466
Capital Expenditure	0
TOTAL DIRECT COST	21466

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PERSONNEL REQUIREMENT (Local)

	No/Pos	Man mon	Amount
A Staff	0	4	1440
B Recrt	0	0	0
C Al frm		3	1350
Sub	0	7	2790
D Sep	0	0	0
E Al to		0	0
Sub	0	0	0
TOTAL	0	7	2790

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LOCAL STAFF ON 1.1.86

Job	No	Man mo	$/mo	Amount
PI M SHAHRIER		4	360	1440
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
TOTAL	0	4		1440

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NEW RECRUITS

Job	No	Man mo	$/mo	Amount
CO-INVESTIGATOR				0
Prof MS Akbar			0	0
				0
TOTAL	0	0		0

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MANPOWER ALLCATED FROM OTHER AREA-LOCAL

Job	Level	Bdg Cd	No/pos	Man mo	$/mo	Amount
G H RABBA	NOB020100		1	3	450	1350

TOTAL				3		1350

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SEPARATIONS

Job	Level	Sep Dt	No/pos	Saved Man mo	$/mo	Amount
						0
						0
						0
TOTAL			0	0		0

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MANPOWER ALLOCATED TO OTHER AREA-LOCAL

Job	Level	Bdg Cd	No/pos	Man mo	$/mo	Amount
						0
						0
						0
TOTAL				0		0

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PERSONNEL - INTERNATIONAL

	No pos	Man mo	Amount
Direct		0	0
Recrt		0	0
Al frm		0	0
Sub		0	0
Sep		0	0
Al to		0	0
Sub		0	0
TOTAL		0	0

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INTERNATIONAL STAFF

Person	Man mo	$/mo	Amount
			0
			0
			0
TOTAL	0		0

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NEW RECRUITS -- INTERNATIONAL

Job	Level	Man mo	$/mo	Join	Amount
					0
					0
TOTAL		0			0

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MANPOWER ALLOCATED FROM OTHER AREA--INTERNATIONAL

Person	Bdg no	Man mo	$/mo	Amount
				0
				0
TOTAL		0		0

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SEPARATIONS OF INTERNATIONAL STAFF

Person	Mo save	$/mo Rep cost	Amount
			0
			0
TOTAL	0		0

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MANPOWER ALLOCATED TO OTHER AREAS--INTERNATIONAL

Person	Bdg no	Man mo	$/mo	Amount

Job	No. of days	Per diem Rate	Per diem Total	Honorarium Rate	Honorarium Total	Travel cost	Amount
			0		0		0
			0		0		0
TOTAL							0

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TRAVEL PLAN -- LOCAL

(calculate on form and enter total)

TOTAL:

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TRAVEL PLANS--INTERNATIONAL

(calculate on form and enter total)

TOTAL:

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SUPPLIES AND MATERIALS

A/C	ITEMS	AMOUNT
3701	Drugs	
3702	Glassware	
3703	Hosp suppl	1000
3704	Stationary	
3705	Chem, media	
3706	Uniform	
3707	Fuel	
3708	Lab suppl	
3709	Housekeep	
3710	Janitorial	
3711	Tool&spares	
3712	Non stock	3000
	SUBTOTAL	4000
3713	FREIGHT	1200
	TOTAL	5200

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OTHER COSTS

A/C	ITEMS	Amount
3800	Maintainence	
3900	Rent,comm,util	
4100	Bank chrges	
4200	Legal	
4300	Print, pub	300
4400	Entertainment	
4500	Service chrges	420
4600	Staff dev	
	TOTAL	720

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INTERDEPARTMENTAL SERVICES

A/C	ITEMS	Amount
4801	Computer	
4802	Trans, Dk	100
4803	Trans,Mtlb	
4804	Water Trans	
4805	Trans,Tknf	
4806	xerox	
4807	Pathology	
4808	Microbiol	1946
4809	Biochem	

4810	X-ray	
4811	I.V.	
4812	Media	
4813	Patient hosp	10710
4814	Animal	
4815	Med Illust	
4817	Telex	
4818	Outpt care	
4830	Trans sub	
	TOTAL	12756

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CAPITAL EXPENSES

Item	Amount
Total	0

CLINICAL TRIAL OF BERBERINE IN CHOLERA AND NON-CHOLERA DIARRHOEA

Data collection sheet

Name of the subject: _____

Hospital admission number: /_/_/_/_/_/

Date of admission to study /_/_/ Day /_/_/ Mon /_/_/ Year

Age in years: /_/_/

Sex: (Male=1, Female=2) /_/

HISTORY AND PHYSICAL:

Admission body weight (kg): /_/_/ /_/_/

Oral temperature (°F): /_/_/_/ /_/_/

Blood pressure (mmHg): Systolic /_/_/_/

Diastolic /_/_/_/

Radial pulse/min: /_/_/_/

Respiration per/min: /_/_/

Duration of diarrhoea before admission (hours): /_/_/

Clinical assessment of dehydration: /_/ (Mild=1, Mod=2, Sev=3)

Previous medication: /_/ (None=1, Yes=2)

Dark-field exam for V. cholerae: /_/ (Positive=1, Neg=2)

Rectal swab culture for V. cholerae:

Admission day /_/ (Pos=1, Neg=2)

Second day /_/ (Pos=1, Neg=2)

Known allergy to Berberine: /_/ (Yes=1, No=2)

DATA RECORD

BASE-LINE STOOL ASSESSMENT (FIRST 4 H OBSERVATION AFTER HYDRATION)

Time started: _____

Time end: _____

Stool volume (ml): /_/_/_/_/

Stool consistency: (Watery=1, Soft=2, semisoft=3, Formed=4) /_/

Urine volune (ml): /_/_/_/_/

Vomit (ml): /_/_/_/

Intravenous fluid given (ml): /_/_/_/_/

Plain water ingested (ml): /_/_/_/

Milk ingested (ml): /_/_/_/

Body weight (kg): /_/_/ /_/_/

Randomization: (Treatment group=1, Control group=2) /_/

Treatment: Berberine given /_/ Note time:

If the subject vomited after the drug administration, please note the time of vomiting occurred: /_/_/ Hours /_/_/ Min

Nausea: /_/

Abdominal pain: /_/

Abdominal discomfort: (Absent=1, Present=2) /_/

Hospital No.: _____

FIRST 8 HOUR POST TREATMENT PERIOD:

Time of collection: _____

OUTPUT:

Stool volume ml:	/_/_/_/_/
Stool consistency: (Watery=1, Semisoft=2, Soft=3, Formed=4)	/_/

INTAKE:

I.V. fluid given (ml):	/_/_/_/_/
Plain water ingested (ml):	/_/_/_/
Urine volume (ml):	/_/_/_/_/
Vomit (ml):	/_/_/_/
Nausea: (Absent=1, Present=2)	/_/
Abdominal pain: (Absent=1, Present=2)	/_/
Abdominal discomfort:	/_/

SECOND 8 HOUR POST TREATMENT PERIOD:

Time of collection: _____

OUTPUT:

Stool volume (ml):	/_/_/_/
Stool consistency: (Watery=1, Semisoft=2, Soft=3, Formed=4)	/_/

INTAKE:

I.V. fluid given (ml):	/_/_/_/_/
Plain water ingested (ml):	/_/_/_/
Urine volume (ml):	/_/_/_/_/
Vomit (ml):	/_/_/_/
Nausea:	/_/
Abdominal pain: (Absent=1, Present=2)	/_/
Abdominal discomfort:	/_/

THIRD 8 HOUR POST TREATMENT PERIOD

Time of collection: _____

OUTPUT:

Stool volume (ml):	/_/_/_/_/
Stool consistency: (Watery=1, Semisoft=2, Soft=3, Formed=4)	/_/

INTAKE:

I.V. fluid given (ml):	/__/__/__/__/
Plain water ingested (ml):	/__/__/__/
Milk ingested (ml):	/__/__/__/
Urine volume (ml):	/__/__/__/
Vomit (ml):	/__/__/__/
Nausea:	/__/
Abdominal pain:	/__/
Abdominal discomfort:	/__/

International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)

CONSENT FORM

Project title: Double-blind random trial of berberine in children with cholera and non-cholera diarrhoea (a collaborative study of ICDDR,B and Dhaka Shishu Hospital).

Investigators: Dr. Hamun Shahrier, Dr. G. M. Rabbani

Description of the research procedures: Your child has watery diarrhoea, either cholera or non-cholera (E. coli) which are usually treated with oral or intravenous rehydration fluids. In cholera but not in non-cholera diarrhoea (E. coli), concurrent treatment with an antibiotic reduces the volume of diarrhoeal stool. However, one of the problems that antibiotics are costly, often difficult to obtain readily and its use causes cholera germs to become resistant. In an attempt to identify a simple, inexpensive and culturally acceptable treatment, we are evaluating the effect of a plant preparation called berberine in treating children with cholera and non-cholera (E. coli) diarrhoea. This drug has been traditionally used as an antidiarrhoeal In India and China and there are no reported side-effects in man. We treated Bangladeshi adults with berberine and have found no unpleasant effects. In this study your child will be admitted to the hospital and will be treated with intravenous fluids (saline) and will eat normally until the illness is over, usually in 3-5 days. Your child will be assigned at random either to treatment group or control group; children in the treatment group will receive berberine sulphate by mouth (10 mg/kg) in 3 divided doses for 3 days while children in the control group will receive identical placebo preparation which has no biological action in man but is given only for experimental comparison. During the hospital stay stool and urine will be collected, measured and examined when necessary. No other specimen such as blood will be collected for examination from your child. The child will be released from the hospital when fully recovered.

POSSIBLE DISCOMFORT OR RISKS: There are no known side-effects of berberine in therapeutic dosage in man. When very large dosages are given this may depress breathing or lower blood pressure. No physical or mental discomfort is to be expected from this drug.

POTENTIAL BENEFITS:

1. This drug could reduce the volume of diarrhoeal stool of your child and thus enhance recovery. The period of hospital stay and the number of vomiting and stooling would also be reduced.
2. Your child will be treated free of cost. There will be no charge for physician fees for any test obtained during the course of the study.
3. As well as the direct benefits to your child, this study will tell us about the clinical usefulness of berberine as an antidiarrhoeal drug and thus bring benefit to other diarrhoeal children who would also require this treatment.

ALTERNATIVES: The only alternative, standard treatment of your child is rehydration fluid and antibiotics in cholera and only rehydration fluid in cases of non-cholera diarrhoea, but no treatment with berberine.

CONSENT (Declaration by the child's parents/guardian): I have been satisfatorily informed of the above described procedures with its possible risks and benefits. My questions were all answered up to my satisfaction and I have been given the opportunity to ask further question regarding the treatment during the study. I'm aware that I am under no obligation to have my child participated in this study and that I am free to withdraw this consent and discontinue participation in this project at any time and it will not affect my child's care. I understand that my child's identity and participation will be kept confidential to the extent permitted by law. If I should have any question, about my child's participation in this project, I will be given an opportunity to discuss in confidence, with a member of the Ethical Review Committee of ICDDR,B.

I give permission for my child's participation in the study.

Investigator's signature_____ Signed_____

Date _____ Date _____