Attachment 1. (9)

Date _____

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. J. Lindenbaum. Trainee Investigator (if any) _____

Application No. 83-604(P) Supporting Agency (if Non-ICDDR,B) _____

Title of Study Digoxin Absorption and Metabolism in Patients with Acute Diarrhoea.

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 NA
   (d) Sensitive questions Yes No NA
   (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 NA
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
   - NA Informed consent form for parent or guardian
   - ✓ Procedure for maintaining confidentiality
   - ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

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

(For: Dr. J. Lindenbaum)
Principal Investigator

Trainee

83-004(P)
25/1/83

SECTION 1 - RESEARCH PROTOCOL

1. Title : Digoxin Absorption and Metabolism in Patients with Acute Diarrhoea.

2. Principal Investigator: Dr. J. Lindenbaum

3. Co-Investigator : Dr. A.N. Alam

4. Starting Date : February 1, 1983

5. Completion Date: March 31, 1983

6. Total Direct Cost : $1,880

7. Scientific Programme Head:

This protocol has been approved by the Nutrition Working Group.

* Signature of Scientific Programme Head : W.R.B.

Date: 25/1/83

This signature implies that the Scientific Programme Head takes responsibility for the planning execution and budget for this particular protocol.

8. Abstract Summary:

Digoxin was found to be metabolized to cardioinactive reduced derivatives (digoxin reduction products, or DRP) that are excreted mainly in the urine (1,2). DRP are formed exclusively by anaerobic bacteria present in the gastrointestinal tract(3), so that urinary DRP excretion after a dose of digoxin is a measure of the functional activity of the anaerobic gut flora in humans. We plan to study digoxin absorption and metabolism in 20 patients admitted to ICDDR,B with acute diarrhoeal illness. Following a single oral dose of lanoxin (0.25 mg), urine will be collected for 48 hours and

..... p. 2

lanoxin & DRP concentrations will be measured by separate radio-immunoassay. As a control group, it is also planned to recruit 100 healthy Bangladeshi adult volunteers to establish the prevalence of DRP excretion in the Bangladeshi population.

9. Reviews :

(a) Research Review Committee: _____

(b) Research Review Committee: _____

(c) Director : _____

(d) B.M.R.C.: _____

(e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION:

1. Objective : The primary aim of this study is to ascertain the absorption and metabolism of digoxin following a test dose of digoxin in acute diarrhoeal patients.

2. Background :

Digoxin is the most widely used cardiac glycoside in the treatment of congestive heart failure and certain arrhythmias. Despite extensive clinical experience, insight into its pharmacokinetics, and the widespread availability of radioimmunoassay measurements of serum concentrations, major problems in the therapeutic use of the drug remain. Digitalis compounds are agents with a low therapeutic ratio. Their use is further complicated in that individual patients vary considerably both in the dosage of digoxin required to produce a beneficial therapeutic effect and in their sensitivity to its toxic effects (1). In addition to interpatient variability, there may be significant fluctuation from time to time in the dosage requirements of a single individual, resulting in therapeutic inefficacy at some times, or digitalis toxicity at others (1,2). The importance of this problem lies not only in the widespread use of cardiac glycosides, but also in their potential for toxicity. Toxic effects of digoxin administration are among the most serious and common adverse drug reactions encountered in clinical medicine (3). Work by many investigators over the past two decades has identified several of the causes of variability in therapeutic response to these agents. Variations in renal function, diffuse myocardial disease, the presence of certain supraventricular arrhythmias, infancy, and interactions with other drugs such as quinidine have all been shown to modify digoxin requirements (2,4). Another major cause of variation that was first identified by our group in 1971 is variability in digoxin absorption from the gastrointestinal tract(5). This problem was recognized after a number of patients at Harlem Hospital Center with atrial fibrillation were found to have high digoxin dosage requirements and relatively low serum digoxin contrations. Significant variation in drug bioavailability from various tablet preparations was found to be

.....p. 2

responsible (5). This was found to be due to differences in tablet dissolution rate (6). As a result of this work, various regulatory agencies have accepted our recommendation (6) that dissolution rate requirements be established for digoxin tablets, and tablets with low dissolution rates and consequent poor bioavailability have been removed from the world market. Impaired digoxin absorption has also been shown to occur during therapy with a number of other drugs such a neomycin, kaolin-pectin, antacids and sulfasalazine, as well as in some patients with malabsorption syndromes (4, 7-9).

Digoxin Metabolism

Despite recognition of factors that may affect digoxin absorption and the removal of poorly absorbed tablets from the market, the problem of marked variability in digoxin therapy persists. Digoxin toxicity remains common; in addition, we frequently continue to encounter patients in whom serum digoxin concentrations are subtherapeutic despite adequate drug dosage and compliance. There is evidence that variation in digoxin metabolism may play an important role in certain patients. It had long been standard teaching that digoxin is excreted largely unchanged, via the urinary tract, and that the small amount of metabolism that occurs, involving the removal of 1, 2 or all 3 of the digitoxose sugars from the molecule and/or its glucuronidation, is of minor clinical significance, since these metabolites remain cardioactive (although digoxigenin is about 1/3 as active as the parent compound) (10, 11). However, it is now recognized that in a significant minority of patients, extensive metabolism of digoxin to dihydrodigoxin, in which the double bond of the lactone ring is reduced, may occur (12-14).

Dihydrodigoxin (and other reduced metabolites, such as the aglycone, dihydrodigoxigenin) have markedly decreased inotropic and toxic effects in various systems, including intact animals, heart-lung preparations, isolated auricles, papil-

digoxin, suggesting a smaller volume of distribution (24). In addition, the compound was rapidly excreted, with mean serum and urinary elimination half-lives of 8.1 ± 1.3 (SEM) and 13.8 ± 2.1 hr, respectively (24). These findings paralleled those reported in cats (21). We then studied 120 patients on chronic digoxin therapy at Harlem Hospital Center and found that 14 (11.7%) excreted more than 40% of total urinary digoxin in the form of reduced metabolites (14).

We then applied the RIA method to the analysis of the patterns of excretion of reduced metabolites in urines obtained from 131 normal subjects who participated in bioavailability studies that were conducted in our laboratory over the past decade (23). Certain striking findings emerged from our retrospective analysis. These included: (1) Delay in metabolite appearance. After a single oral dose of digoxin, peak digoxin excretion occurred during the first 8 hours; in contrast, little or no DRP appeared in the urine during this period, and peak levels were usually achieved at 24-48 hr. (2) Consistency of metabolite formation. Most individuals studied repeatedly over a period of several months to a year consistently excreted or failed to excrete reduced metabolites. The 131 subjects could be divided into two groups on the basis of their response to their first exposure to digoxin. The majority (approximately 2/3) excreted 0 to 5% DRP (calculated as DRP divided by the total excretion of digoxin and its metabolites X 100), with 5% being the lower limit of accurate detection under routine conditions of the assay; they are referred to as "non-excretors". One-third of the subjects excreted between 5 and 70% DRP, with 1 in 10 excreting more than 40%; they are referred to as "excretors". With subsequent exposures to digoxin, regardless of the number of single or steady state doses given, more than 90% of subjects remained in their original category as excretors or non-excretors. (3) Occasional disappearance of the tendency to reduce digoxin. An important finding was an exception to the rule: 6 subjects who had repeatedly formed large amounts of DRP no longer excreted any

detectable DRP on subsequent repeated exposure to the drug. This indicated that environmental factors must in part determine variability in metabolite production. (4) DRP formation appeared to vary inversely with bioavailability. In those excretor subjects who received two digoxin preparations of differing bioavailability, greater DRP excretion usually occurred with the preparation that was absorbed less well. In two DRP excretors who received digoxin by both the oral and intravenous route, DRP excretion was greater after oral administration. (5) Change in DRP excretion after antibiotic therapy. A provocative observation was the disappearance of DRP formation in two excretor subjects who by chance had each taken a brief course of erythromycin for an upper respiratory tract infection over a two week period between digoxin doses.

Although these retrospective findings were not definitive, they provided potential clues that allowed us to form hypotheses that could be more rigorously tested by prospective experiments. We speculated that the inverse relationship of DRP formation to bioavailability indicated a gastrointestinal site of metabolite formation, possibly in the colon, in view of our finding of maximal dihydrodigoxin formation on the second day after an oral dose of digoxin; that this metabolism was an activity of the colonic bacterial flora, which might vary from time to time in a given person and which was sensitive to the effects of antibiotic therapy. The reason why most people did not form reduced metabolites, and a minority did, could be due to differences in their enteric flora. We then tested these hypotheses in planned, prospective in vivo and in vitro experiments. We first showed that by intentionally varying the bioavailability of the digoxin preparation administered, we could markedly alter the extent of DRP formation in excretor subjects under steady state conditions (25). We then attempted to show that cultures of the fecal flora of excretor subjects could convert digoxin to DRP in vitro. Stool samples were obtained from 30 normal volunteers

who excreted 15-70% DRP in vivo when given one or more oral doses of digoxin. One gram aliquots of stool were incubated in pre-reduced anaerobic media containing digoxin 10 ug/ml for 48-96 hours under anerobic conditions. In 29 of the 30 subjects studied, 90 to 100% of the digoxin originally present was converted to DRP. The pre-addition of erythromycin or clindamycin at concentrations of 1 to 5 ug/ml, or of tetracycline at 50 ug/ml, markedly or completely inhibited DRP formation by the stool cultures (25).

Having demonstrated that bacteria capable of metabolizing digoxin were present in excretor subjects, we then studied the effect of antibiotics on the tendency to form DRP in vivo. Three known excretors were placed on 0.5 mg digoxin in tablet form daily for 10-17 days and then given a 5-day course of erythromycin or tetracycline. Digoxin was continued throughout antibiotic therapy and for the following week. In each subject a dramatic fall in DRP excretion occurred during the first 48 hours of antibiotic therapy. Reduced metabolites, which were at a level of 30-65% in the urine before therapy, fell to undetectable or barely detectable (less then 2%) levels in each volunteer by the fifth day of antibiotic therapy and remained at those levels during the subsequent week. Stool specimens from each subject contained both digoxin and DRP before antibiotics, but only digoxin after. Steady state serum digoxin concentrations, obtained on 3 consecutive days before and after antimicrobial treatment, rose in each subject, approximately to double baseline values in two of them (25).

These experiments appeared to show that (1) DRP were made by antibiotic sensitive bacteria in the gastrointestinal tract (2) this was the only important site of DRP formation, in view of the disappearance or virtual disappearance of the metabolites after antibiotics and (3) changes in the enteric flora may markedly alter the state of digitalization.

Identification of DRP-forming bacteria

We then set out to isolate the organism responsible for DRP production by the human gut flora (14). Of more than 400 colonies of organisms isolated from the stool of two excretor subjects, only two were found to produce DRP. Both were identified as Eubacterium lentum, an anaerobic non-sporeforming gram positive rod frequently but not universally found in the human gut flora (14). We have also tested 150 stock strains of anaerobes and aerobes representative of the normal gut flora. The only organisms found to elaborate DRP were strains of E. lentum (14). Of 28 strains of E. lentum that we have tested, 18 made DRP. It thus appears that a subset of a single species of bacteria found in the human gastrointestinal tract is responsible for the conversion of digoxin to its reduced metabolites (14). We have also recently found that a substantial minority of non-excretor subjects contain bacteria in their stool in high concentration that are capable of converting digoxin to DRP in vitro (despite the fact that this process does not occur in vivo) (14). Five DRP-forming organisms isolated from stool cultures obtained from two non-excretor subjects were also identified as Eubacterium lentum. It is apparent, then, that neither the presence of DRP-forming organisms, nor their concentration in stool, is the determining factor as to whether a person given digoxin will form reduced metabolites in vivo.

In summary, then, a substantial minority of patients receiving digoxin convert a fraction of the drug to cardioinactive reduced metabolites. In approximately 10% of patients, conversion is massive (i.e., more than 40% urinary DRP excretion) and potentially of clinical significance. Our work over the past three years has shown that DRP excretors and non-excretors tend to remain in the same category regarding their tendency to form these metabolites; that DRP are made in the gastrointestinal tract as the result of the action of enteric bacteria; that this process appears to be mediated by Eubacterium lentum, a frequent constituent

of the normal gut flora; and that therapy with certain antibiotics may reverse this process and lead to increments in the amount of circulating digoxin.

Changes in the Colonic Flora with Acute Enteritis

A number of investigators have reported changes in the composition of the human gut flora during acute infectious enteritides. In patients with cholera (26), enterotoxigenic E. coli infections (27), and other non-vibrio acute diarrheas (27, 28), marked shifts in the normally predominantly anaerobic fecal flora (29) have been reported. During acute diarrhea in these patients, facultative aerobic organisms predominated in the stool, and the concentration of anaerobes, such as Bacteroides, was strikingly diminished (1- to 5-fold log decrements in concentration). Follow-up studies 4 to 10 days after onset of these illnesses showed a gradual return to the normal balance of fecal organisms (26, 27). Similar findings were reported in some, but not all, human volunteers in whom diarrhea was induced by the administration of saline via a small intestinal tube (30). All of these studies were performed before Eubacterium lentum was well characterized as a major component of the human intestinal flora, and the effect of diarrheal states on the concentration and acitivity of Eubacteria has not been reported.

We propose to study digoxin absorption and metabolism in patients during and after recovery from acute diarrhea due to a variety of infectious causes.

Acute diarrheal illness has been reported in isolated case reports to cause a fall in serum digoxin concentrations in previously well digitalized patients (31, 32). Digoxin malabsorption has been reported in some but not all patients with a variety of malabsorption syndromes (8, 9). It is possible that digoxin metabolism would be enhanced as a result of an acute diarrheal illness, in view of the inverse relationship between digoxin absorption and its metabolism by the flora of the lower intestine. On the other hand, the acute suppression of the anaerobic flora of the large bowel that has been documented with acute infec-

tious diarrheas may also involve Eubacterium lentum, in which case digoxin metabolism would be suppressed. In the latter instance, a digitalized patient who developed acute diarrhoea would be at risk for digoxin toxicity, since suppression of the anaerobic flora in a DRP excretor may result in substantial increments in serum digoxin concentration (25).

B. Specific aims:

(i) To determine the urinary concentrations of digoxin and its cardioinactive reduced derivatives (DRP) in patients with acute diarrhoea of varied etiology, and

(ii) to understand better the absorption and metabolism of digoxin in acute enteritis where the anaerobic gut flora e.g, Eubacterium lentum,responsible for DRP production in humans, may be disturbed.

Methods of procedures

It is planned to study digoxin absorption in 20 patients seen at the ICDDR,Bangladesh for acute diarrheal illness. Only adults who are able to give informed consent will be studied. The absorption and metabolism of a single 0.25 mg dose of digoxin in tablet form will be tested. A digoxin preparation of rapid dissolution rate and high bioavailability (standard Burroughs Wellcome Lanoxin tablets) will be given. Urine will be collected for two consecutive 24 hour periods after the dose, and digoxin and DRP concentrations measured by separate radioimmunoassys (24,33) in Dr. Lindenbaum's laboratory at Columbia University. We have previously established that a 48 hour urine collection suffices as a measure of both digoxin absorption and metabolism in normal volunteers (Lindenbaum, J: unpublished). To be certain of the validity of this in patients with diarrhea, in selected patients who need to be hospitalized beyond 48 hours, urine collections will be extended to include up to 6 days after the dose. The patients will be restudied approximately 10 days and 2 months after recovery from the acute diarrheal episode. In general, patients who are not given antibiotics will be studied.

In selected patients, serial dilutions of stool specimens obtained during and after recovery from acute diarrhoea will be incubated in a "pre-reduced" anaerobic broth containing digoxin 10 ug/ml for 48 hr and supernatant fluid tested for the production of DRP, as well as residual digoxin, by our radioimmunoassays.

In addition, it is proposed to study one or more normal control groups from the Bangladeshi population to establish the frequency of DRP excretion in Bangladeshis. The only populations studied to date have been white and black Americans, in whom the prevalence of DRP excretion (as measured in urine

obtained after a test dose of digoxin) has been found to be of the order of 33-40% (14,23). It is proposed to study 100 normal healthy Bangladeshi adults, possibly employees of ICDDR,Bangladesh who volunteer to participate. After informed consent is obtained, 0.25 mg of digoxin will be given by mouth and urine collected for 48 hrs. If possible, we would also like to study normal Bangladeshi population groups in whom strict vegetarianism is a practice, if such groups are available, in order to obtain information about the effect of diet on the human anaerobic gut flora.

The dose of digoxin to be used, 0.25 mg, should be free of significant risk in the patients and normal volunteers to be studied. Occasionally transient nausea (without vomiting) has been seen in normal individuals with this nondigitalizing dose. However, no serious arrhythmias or other notable side effects have been encountered by us in over 300 normal subjects studied over the past 12 years, or have been reported in the very extensive literature on digoxin.

Only previously healthy subjects with no history of chronic illness, renal disease, heart disease, or recent therapy with cardioactive drugs, will be studied. Patients with severe dehydration, uncorrected electrolyte disturbances, elevated serum creatinin, chronic renal disease or subnormal urine output will be excluded, as will patients who are vomiting. The patients and the control subjects will be informed by one of the investigators of the research nature of the study and will not be coerced in any manner to participate.

The performance of the study will not interfere in any way with any

planned therapy for the patients (e.g., oral rehydration). 2 ml of venous blood will be required for determination of serum electrolytes, serum creatinin, plasma sp.gr. etc. Stool samples will be collected for M/E and culture & sensitivity. An E.C.G. will be done in the study patients to exclude any major cardiac abnormality.

Significance :

The Proposed study would shed light on the biologic behavior of the human anaerobic gut flora during and after intestinal infections as well as provide valuable information concerning the proper use and dosage of cardiac glycoside drugs in patients with diarrhoeal disease.

FACILITIES REQUIRED :

Patients will be admitted in the present study ward of ICDDR,B. Laboratory facilities in the clinical pathology, biochemistry and microbiology department will be utilized. Radioimmunoassys will be done in Dr. Lindenbaum's laboratory at Columbia University, New York. No new equipment or other resources will be required.

References

1. Craig LC, Lown B, Levine SA. JAMA 166:2139, 1958.
2. Butler VP, Lindenbaum J. Amer J Med 58:460, 1975.
3. Smith TW. Amer J Med 58:470, 1975.
4. Brown DD, Spector R. Juhl RP. Drugs 20:198, 1980.
5. Lindenbaum J, Mellow MH, Blackstone MD, Butler VP. NEJM 285;1344, 1971.
6. Lindenbaum J. Butler VP, Murphy JE, Cresswell RM. Lancet 1:1215, 1973.
7. Lindenbaum J, Maulitz RM, Butler VP. Gastroenterology 71:394, 1976.
8. Heizer WD, Smith TW, Goldfinger SE. NEJM 285;257, 1971.
9. Gerson CD, Lowe EH, Lindenbaum J. Amer J Med 69;43, 1980.
10. Marcus FI, Kapidia GJ, Kapadia GG. J Pharmacol Exp Ther 145:203, 1964.
11. Doherty JE, de Soyza N, Kane JJ, Bissett JK, Murphy ML. Progr Cardiov Dis 21:141, 1978.
12. Peters U, Falk LC, Kalman SM. Arch Intern Med 138:1074, 1978.
13. Greenwood H, Snedden W, Hayward RP, Landon J. Clin Chim Acta 62:213, 1975.
14. Dobkin JF, Saha JR, Butler VP, Neu HC, Lindenbaum J. Trans Assoc Am Phys, 1983, in press.
15. Vick RL, Kahn JB, Acheson GH. J. Pharmacol Exp Ther 121:330, 1957.
16. Bach EJ, Reiter M. Naunyn-Schmied Arch Exp Path Pharmak 248:437, 1964.
17. Brown BT, Stafford A, Wright SE. Brit J Pharmacol, 18:311, 1962.
18. Okamma TB, Tramell P, Kalman SM. J Pharmacol Exp Ther 183:559, 1972.
19. Erdmann, E, Schoner W. Naunyn-Schmied Arch Exp Path Pharmacol 283:335, 1974.
20. Marcus FI, Ryan JN, Stafford MG. J Lab Clin Med 85:610, 1975.
21. Heinz N, Flasch H. Naunyn-Schmied Arch Pharmacol 303:181, 1978.
22. Luchi RJ, Gruber JW. Amer J Med 45:322, 1968.
23. Lindenbaum J, Tse-Eng D, Butler VP, Rund DG. Amer J Med 71:67, 1981.
24. Butler VP, Tse-Eng D, Lindenbaum J, et al. J Pharmacol Exp Ther 221:123, 1982.
25. Lindenbaum J, Rund DG, Butler VP, Tse-Eng D, Saha JR. NEJM 305:789, 1981.
26. Gorbach SL, Banwell JG, Jacobs, Chatterjea BD, Mitra R, Brigham KL, Neogy KN. J Infectious Dis 121:32, 1970.

References, cont'd.

27. Gorbach SL, Banwell JG, Chatterjee BD, Jacobs B, Sack RB. J Clin Invest 50:881, 1971.

28. Moore WEC, Cato EP, Holdeman LV. J Infectious Dis 119:641, 1969.

29. Simon GL, Gorbach SL. Intestinal flora in health and disease. In: Physiology of the Gastrointestinal Tract, ed. LR Johnson, Raven Press, New York, 1981, pp 1361-1380.

30. Gorbach SL, Neale G, Levitan R, Hepner GW. Gut 11:1, 1970.

31. Jusko WB, Conti DR, Molson A, et al. JAMA 230:1554, 1974.

32. Koup JR, Tobias DE. Drug Intelligence Clin Pharmacy 8:644, 1974.

33. Smith TW, Butler VP, Haber E. NEJM 281:1212, 1969.

SECTION III - BUDGET

A. Detailed Budget

1. Personnel :

Name	Position	% Effort	Taka	$
Dr. J. Lindenbaum	Principal Investigator	-	No cost to ICDDR,B	
Dr. A.N. Alam	Co-Investigator	20%	9334	

2. Supplies and Materials :

Lab Tests(Plasma sp.gr., electrolytes, creatinin)	1000
Plastic containers for collection of urine	4000
Urine analysis	175
Stool M/E	52
Stool culture	375

RIA for Digoxin & DRP: To be done in Dr. Lindenbaum's laboratory.

E.C.G.	1250

Lanoxin: to be provided by the courtesy of Burroughs Wellcome Co.

3. Equipment - Nil

4. Hospitalisation cost:
120 patients days
120 x Tk. 150/day — 18000

5. Outpatient care : Nil

6. ICDDR,B transport : Nil

7. Transportation of material : Nil

8. Rent, Communication, Utilities: Nil

9. Printing and Reproduction: Nil

10. Contractual services: Nil

11. Construction : Nil

	Tk.	34,186
	($ 1 = Tk. 20)	
10% overhead cost $ 1710		$1,710

GRAND TOTAL = $1880

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. 20 adult patients (age > 17 yrs) with acute diarrhoea attending the outpatient department of ICDDR,B will be admitted into the study ward.
2. There is no potential risk involved in the study.
3. Not applicable.
4. All records will be kept strictly confidential. They will remain with the Principal Investigator. If data is put on computer tapes, study patients will be referred to by number only.
5. Informed consent (signed or thumb impression) from patients or their guardians will be obtained prior to the study. There is no procedure in this study which may unmask the privacy of the subject.
6. Interview will be taken only related to their medical and personal history and is needed to assess the condition of the patients. Five minutes will be enough for such interview.
7. This study will yield valuable information on the biologic behaviour of the human anaerobic gut flora during and after acute intestinal infections. The patient will gain by the treatment of his illness and the society will gain if a correct information concerning the dosage of cardiac glycoside drugs in patients with diarrhoeal disease could be obtained.
8. This study will require examination of blood (2 cc only), stool, urine once after admission.

   The patients will be followed up 10 days and 2 months after recovery from the acute diarrhoeal episode when only 48 hrs urine collection will be made following a single dose of cardiac glycoside as before.

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH

CONSENT FORM

The ICDDR,B is carrying out research to develop better methods for improved management of diarrhoeal diseases. Appropriate management of a digitalised patient who develop diarrhoea is one aspect of the problem. In such patients, digoxin toxicity may occur. This study will help us to determine the appropriate dosage of cardiac glycosides in patients developing acute diarrhoea.

We hope that you will participate in the study for the greater wellbeing of the society. If you agree to participate in the study the following measures will be taken :

1. You will be given best possible care for diarrhoea.
2. You will have to stay at least for 2 days in the hospital. Again, you will have to come back first after 10 days and later after 2 months. You will have to stay for 2 days each on these visits.
3. On the first day 2 cc venous blood will be taken for examination. Besides, stool and urine examination will be done, as routine. one 0.25 mg Lanoxin Tablet will be given and 48 hrs. urine will be collected. On the follow-up visits 48 hrs. urine will be examined only after ingestion of 0.25 mg of Lanoxin Tablet.
4. You will be given appropriate drugs at the time of discharge and follow ups.
5. You will receive appropriate treatment even if you do not participate in the study. You are at liberty to withdraw at any time from the study and this in no way will hamper your treatment in the hospital.

If you are voluntarily willing to participate in the study, please give signature/left thumb impression below :

Signature of Investigator with date.	Signature/ Thumb Impression of the patient.

সম্মতি পত্র

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র, ঢাকা ডাইরিয়া রোগের উন্নততর চিকিৎসা উদ্ভাবনের জন্য গবেষণা চালিয়ে যাচ্ছে। যে সব রোগী ডিজিটালাইস পায় এবং ডাইরিয়ায় আক্রান্ত হয় তাহাদের সঠিক চিকিৎসা প্রণালী উদ্ভাবনের জন্য চেষ্টা চলছে। এইসব রোগীদের ডিজক্সিনের মাত্রাতিরিক্ততার কারণে বিষক্রিয়া হতে পারে। এই গবেষণার মাধ্যমে আমরা এই সব রোগীদের জন্য ডিজক্সিনের সঠিক মাত্রা উদ্ভাবন করতে পারি।

আমরা আশা করি, সমাজের বৃহত্তর স্বার্থে আপনি এই গবেষণায় অংশগ্রহণ করবেন। আপনি যদি রাজী থাকেন তাহ'লে নিম্নলিখিত ব্যবস্থাদি নেয়া হবে-

১। আপনাকে ডাইরিয়ার জন্য সর্বোত্তম চিকিৎসা দেয়া হবে।

২। আপনাকে কমপক্ষে ২ দিন হাসপাতালে ভর্তি থাকতে হবে। এছাড়া ১০ দিন পরে একবার এবং ২ মাস পরে একবার আপনাকে হাসপাতালে ফিরে আসতে হবে। প্রত্যেকবারই ২ দিন করে হাসপাতালে থাকতে হবে।

৩। ভর্তির পর ২ সি, সি, শিরার রক্ত পরীক্ষার জন্য নেয়া হবে। এছাড়া নিয়মমাফিক মল, মূত্র পরীক্ষা করা হবে। ০°২৫ মিঃ গ্রাঃ ল্যানোক্সিন ট্যাবলেট খাওয়ানো হবে এবং ৪৮ ঘন্টার মূত্র সংগ্রহ করা হবে পরীক্ষার জন্য। ফিরতি আগমনের সময়ে ও এই পরীক্ষা পুণর্বার করা হবে।

৪। আপনাকে ছুটির সময়ে প্রয়োজনীয় ঔষধ দেয়া হবে।

৫। আপনি যদি অংশগ্রহণ নাও করেন তবুও চিকিৎসার কোন ত্রুটি হবে না। আপনি গবেষণা চলাকালীন যে কোন সময়ে ইচ্ছা করলে আপনার নাম প্রত্যাহার করতে পারেন। এতে আপনার যথোপযুক্ত চিকিৎসার কোন অসুবিধা হবে না।

আপনি যদি স্বেচ্ছায় গবেষণায় অংশগ্রহণ করতে রাজী থাকেন, তাহ'লে নীচে আপনার স্বাক্ষর কিংবা বাম বৃদ্ধাংগুলের ছাপ দিন।

ধন্যবাদ -

গবেষকের স্বাক্ষর এবং তারিখ

রোগী/অভিভাবকের স্বাক্ষর/ছাপ