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Attachment 1.

Date 19-8-82

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. Iqbal Kabir

Trainee Investigator (if any) _____

Application No. 82-038

Supporting Agency (if Non-ICDDR,B) _____

Title of Study Comparative efficacy of Ceftriaxone and Ampicillin given as a Single dose for the treatment of Acute shigellosis

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
5. Will signed consent form be required:
   (a) From subjects — (Yes) No
   (b) From parent or guardian (if subjects are minors) — Yes No (NA)
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith to Committee:
   - NA 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
   - NA 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.

Kabir
Principal Investigator

Trainee

82-038
23/8/82

SECTION I - RESEARCH PROTOCOL

1. Title: Comparative Efficacies of Ceftriaxone and Ampicillin given as single doses for the treatment of acute Shigellosis

2. Principal Investigator: Dr. Iqbal Kabir

   Co-Investigators: Dr. Asma Khanam, Dr. S.Q. Akhtar, Dr. Thomas Butler, Dr. Syed Masud Ahmed

3. Starting Date: October 1982

4. Completion Date: January 1983

5. Total Direct Cost: $ 12,644

6. Scientific Program Head:

   This protocol has been approved by the Pathogenesis & Therapy Working Group.

   Signature of the Scientific Program Head: Thomas Butler

   Date: 19-8-82

7. Abstract Summary:

Shigellosis is one of the most common and clinically severe causes of diarrhea in Bangladesh and other developing countries. Antibiotic resistance in Shigella species emerges rapidly in a human population being exposed to antibiotics, and already about 20% of Shigella isolates in Dacca are resistant to ampicillin, indicating the need to evaluate newer antibiotics for possible future use. A new antibiotic ceftriaxone, which is a cephalosporin derivative, is more potent against Gram-negative bacteria than are older betalactam antibiotics. This study proposes to compare single dose therapies of ceftriaxone (1g) and ampicillin (4g) given intravenously to 20 adult males in each group with shigellosis. The clinical courses and antibacterial effect on fecal Shigella will be compared.

8. Reviews:

a. Research Involving Human Subjects: _____

b. Research Review Committee: _____

c. Director: _____

d. B M R C: _____

e. Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objectives:

a. To compare the clinical efficacies of single dose ceftriaxone and ampicillin treatment in patients with shigellosis.

b. To compare the Bacteriological effects of ceftriaxone and ampicillin in shigellosis in vivo by eradication of bacteria from stool and in vitro by laboratory sensitivity testing.

2. Background

SHIGELLA is a common cause of diarrhea in both epidemic and isolated situations. Although this organism can be isolated from stool of asymptomatic persons, it generally causes an illness that manifests clinically as dysentery or an enterotoxin-like diarrhea. Several antibiotics have been successful in eradicating clinical symptoms and fecal shedding; however, changing sensitivity patterns make the initial selection of antimicrobial therapy difficult.

In Bangladesh, ampicillin is widely regarded as the drug of first choice. In 1980, about 95% of isolated Shigellae were sensitive to ampicillin. At the ICDDR,B Gilman and co-workers[1] evaluated ampicillin as a single dose therapy and found that adults and children over 4 yr old responded as well to a single dose of 100 mg/kg as to the conventional 5-day course. In the intervening yeras, however, the frequency of ampicillin-resistance in isolated Shigellae at the ICDDR,B has risen to 20%, indicating the need to evaluate new antibiotics.

Ceftriaxone is a newly developed semi-synthetic cephalosporin beta-lactam antibiotic. The main advantages of ceftriaxone over other beta-lactam antibiotics are the increased potency against Gram-negative bacteria and the prolonged half-life in the serum following injection. All strains of Shigella and Salmonell athat have been tested were susceptible with minimum inhibitory concentrations of 0.1 ug/ml or less[2,3].

The serum half-life of ceftriaxone in man is about 8 hr, compared to about 1 hr for ampicillin[4]. Thus, ceftriaxone would be expected to be more active over alonger time following a dose, suggesting that less frequent administration and even single-dose treatments would be effective.

Another potential advantage of ceftriaxone for shigellosis in Bangladesh is its resistant to beta-lactamases[5]. Thus, the resistance to ampicillin, which occurs in about 20% of our Shigella strains and is mediated by beta-lactamase, could be counteracted by ceftriaxone.

Until 3 human studies were done with ceftriaxone Kellar et al treated severe respiration tract infection found it was safe and effective. Ceftriaxone has been used in human with a variety of bacterial infections and was safe and effective[6]. Epstein et al treated 34 patients with bacterial injections, 12 had skin and soft tissue injection, 10 had urinary tract infection, 8 had pneumonia, 2 had biliary tract infection, one had sinusitis, one had diverticulis. The bacteria isolated included both gram positive and gram negative bacteria. Response rate was 91%. Adverse reactions will monitored and were encountered in eight patients. None of these patients were serious enough to discontinue the therapy. Five had phlebitis at the injection site. Two had fever 38°O - 38.5°C for 1 weak but temp. came down within 36 hrs after discontinuing the therapy one of the patient complained of dizziness during therapy.

3. Rationale

Shigellosis continues to be a major cause of diarrhea and dysentery in Bangladesh. In particular in children, shigellosis is a leading contributing cause of death. Antibiotic resistance has emerged in Shigella strains in Dacca, and now about 20% of strains are resistant to ampicillin. There is a need to evaluate new antibiotics which offer promise of curing shigellosis when in the future our presently available drugs may become ineffective due to resistance.

B. SPECIFIC AIMS:

1. In a randomized clinical trial of shigellosis to compare the efficacies of ceftriaxone and ampicillin given as single doses to relieve symptoms and signs of illness.

2. To compare the antibiotic efficacies of ceftriaxone and ampicillin by in vitro testing and by testing the time after treatment that viable Shigellae are eliminated from the stool.

C. METHODS OF PROCEDURE:

1. Patient selection: Only males over 15 years old will be considered. About 60 patients will be selected in order to obtain 40 confirmed cases of shigellosis, Patients should have the recent onset, 2 days or less, of diarrhea defined as 3 or more loose motions per day. In addition, they should have at least two of the following symptoms: fever, chills, abdominal pain, tenesmus, passage of mucus, passage of blood. They must state that they are not allergic to penicillin drugs. Patients

meeting these criteria will be screened with a stool microscopic examination; those showing ≥ 20 WBC per HPF and showing an absence of hematophagous Entameoba histolytica will be selected.

2. Informed consent: Patients selected will be explained the nature of the study and the alternative course of not enrolling. Those agreeing will be asked to signed the Informed Consent form.

3. Baseline data before treatment: For the 24-hr period before admission the patients will be asked the number of stools passed, presence of blood or mucus, abdominal pain, tenesmus, fever, and chills. Two freshly passed stools will be cultured for Shigella. The species and antibiotic sensitivity to ampicillin and ceftriaxone will be determined. Rectal temperatures every 8-hr will be taken.

4. Randomization: Patients will be given serial numbers in the order they are selected. From a table of random numbers the patients will be assigned to receive either ceftriaxone 1 gm or ampicillin 4 gm intravenously. The code sheet of numbers will be kept by Dr. Butler. Both the physicians selecting patients and the clinical research staff recording data will be unaware which treatment group the particular patients are in. The study will be continued until 20 patients with confirmed Shigella have been assigned to each group.

5. Clincial data: After the drug treatment has been given, patients will be kept in the hospital for 7 days and fed a normal diet and given ORS to match approximately fluid losses. At the end of each 24-hr period, each patient will be asked the number of stools passed during the 24-hr

period, presence of fever, chills, abdominal pain, tenesmus, blood, and mucus. Rectal temperatures will be recorded every 8-hr. Two freshly passed stools will be cultured daily for Shigella.

6. Data analysis: Complete data sheets will be kept. At the end of the study, confirmed cases of Shigellosis will be analyzed. Means and standard deviations of measurements will be calculated and frequencies of symptomatology recorded. Comparisons will be made by student's T tests and Chi-square tests.

D. SIGNIFICANCE

Testing new antibiotics in shigellosis may reveal that new agents are satisfactory alternatives to ampicillin, and these agents could be used if ampicillin resistance becomes more prevalent. If newer antibiotics are shown to be clinically or microbiologically superior to ampicillin, then these drugs can be examined further as possible drugs of first choice.

E. FACILITIES REQUIRED

The clinical research ward and laboratories at ICDDR,B will be adequate for this research.

F. COLLABORATIVE ARRANGEMENTS

The Roche Foundation will provide both ceftriaxone and ampicillin for injection and will provide antibiotic discs for sensitivity testing.

ABSTRACT SUMMARY

Comparative efficacy of Ceftriaxone and Ampicillin given as a single dose in acute Shigellosis

1. This study will require 60 adult male patients who has bloody dysentery with acute onset. Thirty patients will get Ampicillin trihydrate 4 gm and another 30 patients will get Ceftriaxone 1 gm in a single dose intravenously. Comparison will be done on clinically and bacteriologically cure.

2. Patients will be treated with Ampicillin and Ceftriaxone (a new cephalosporin) which are safe drugs. Each patients will be asked about Penicellin hypersensitivity and if any will not be taken into the study. Regarding other minor side effects, local pain, they will be carefully examined every day by a physician. There is no psychological, social and legal risk to patients included in this study.

3. Detailed medical history and careful physical examination will be done every day to see the clinical improvement.

4. Confidentiality will be maintained, and all data will be abreviated and will be published without reference to the subject's name and identity.

5. Informed consents will be obtained from the patients.

6. No personal interview except relevant history of illness will be taken.

7. The direct benefit to the subject will be the cost free treatment. The long term social benefit will be to find out a suitable new antibiotic given as a single dose where multiple antibiotic resistance to Shigella sp. is frequently encountered. As the drug will be given as single dose it will be most cost effective form of therapy and practically feasible.

8. No hospital records except clinical data will be analysed. Only stool and blood specimens will be required.

REFERENCES

1. Gilman, R.H., Spira, W., Rabbani, H., Ahmed, W., Islam, A., Rahaman, M.M. Single-dose ampicillin therapy for severe shigellosis in Bangladesh. J. Infect. Dis. 143: 164, 1981.

2. Angehrun, P., Probst, P.J., Reiner, R. and R. Then. Ro 13-9904, a long acting broad-spectrum cephalosporin: in vitro and in vivo studyes. Antimicro. Agents Chembother. 18: 913-921, 1980.

3. Clarke, A.M. and S.J.V. Zemocov. 1981. Ro 13-9904 and GR 20263, two new cephaloscorins with broad-spectrum activity: an in vitro comparison with other B-lactam antibiotics. J. Antimicrob. Chemotherapy 7:515-520.

4. Reiner, R., Weiss, U., Brombucher, P. Lanz, Montavon, M., Furlenmeier,P. Angehrun, P.J. Probst. Ro 13-9904/001, a novel and long-acting parenteral cephalosporin. J. Antibiot. 33: 783-786.

5. Neu, H.C., N.J. Meropol, and K.P. Fu. 1981. Antibacterial activity of ceftriaxone (Ro 13-9904), B-lactamase-stable caphalosprin. Antimictob. Agents Chemother. 19: 414 - 432.

6. Epstein, J.S., Hasselquist, S.M., Simon, G.L. Efficacy of ceftriaxone in serious bacterial infections. Antimicr. Agents Chemother 21:402,1982.

7. Anton, P.A., Kemp, J.A.? Butler, T., Jacobs, M.R. Comparative efficacies of ceftriaxone, moxalactam, and ampicillin in experimental Salmonella typhimurium infection. Antimicr. Agents Chemother (in press) 1982.

8. Kellar, R. and L. Humair 1981. Treatment of severe respiratory Tract Infection with ceftriaxone (Ro 13-9904). A pilot study. Chemotherapy (Basel) 27 (supple 1) 93-94.

9. Patel, I.H.K. Miller, R. Weinfeld and J. Spice handler, 1981. Multiple Intravenous dose; pharmacokinetics of ceftriaxone in man. Chemotherapy (Basel) 27 (Supple I) 47-56.

SECTION III - BUDGET

A. DETAILED BUDGET

1. Personnel services:

Name	Position	%Effort	Taka	Dollar
Dr. I. Kabir	Pr. Investigator	50 %	13,500	-
Dr. T. Butler	Co - Investigator	15 %		5,010
Dr. A. Khanam	Co - Investigator	25 %	7,425	-
Dr. S.Q. Akhtar	Microbiologist	10 %	2,970	-
Dr. S. Masud Ahmed	Research Fellow	25 %	2,875	-
Study Nurse	4 person month	25 %	8,832	-
Mizanur Rahman	Clin.Pathologist	50 %	5,155	-
		Sub Total	;40,757	5,010

2. Supplies and materials:

1. Ceftriazone and ampicillin supplied by Roche - No cost to ICDDR,B

2.

Laboratory test	No of test	Cost/Test	Tk.		
C B C	60	5.20	312.00		
Blood elect	60	12.00	720.00		
Stool Micro	180	2.50	450.00		
Stool swab cult	840	10.00	8,400.00		
Urine analysis	60	2.50	150.00	10,032	-

3. Misc: Vermox tab, Flagyl, Farsolate etc.. 2,000 -

Sub Total :12,032 0

3. Equipment:

One Scientific calculator (Casio fx 39) 800 -

4. Patient hospitalization:

7 days fo 80 patients: Tk.150/1 patient 84,000 -

Sub Total: 84,800 0

5.	O.D.P. Care: None		
6.	ICDDR,B transport:		
	30 miles x 60 x 4.50	8,100	-
7.	Travel & transportation: None		
8.	Transportation of things: None		
9.	Rent and communication: None		
10.	Printing and reproduction:	5,000	100.
11.	Construction: None		
12.	Others: None		
	Grand Total	Tk.150,689	5,110
		(US$ 7,535)	
		5,110	
	Total :	US$12,645	

(Conversion rate US$1 = Tk.20)

BUDGET SUMMARY

		Dollar
1.	Personnel Services	7,048
2.	Supplies and Materials	601
3.	Equipment	40
4.	Patient hospitalization	4,200
5.	ODP Care	-
6.	ICDDR,B transport	405
7.	Travel and transportation	-
8.	Transportation of things	-
9.	Rent and communication	-
10.	Printing and reproduction	350
11.	Construction	-
12.	Others	-
	Grand Total :	12,644

Consent Form

Ceftriaxone study

Diarrhoea due to Shigellosis continues to be a major problem in Bangladesh. During last few years there was significant increase in resistance of Shigella sp. to multiple antibiotic including Ampicillin. In our study we are trying to find out a new suitable antibiotic to counteract that. Ceftriaxone was found to be highly effective against may enterobacteriocae, including Shigella when tried in vitro. Human study has also shown that there was no adverse reaction to this new drug. We shall give you either Ampicillin 4 gm or Ceftriaxone 1 gm in a single intravenous dose and compare the efficacy of those two drugs. You will have to stay here for 7 days and 1 c.c. of blood will be taken to see Total WBC and Hct. That amount of blood would have been required even on normal treatment.

You have every right to refuse to enter the study and you can stay out of the study any time and your normal treatment will not be hempered.

If you are fully agreed. Please sign. it.

Thanks.

_____
Signature of Investigator

_____
Signature/Left Thumb Impression
of patient's Guardian.

Date: _____

সম্মতি পত্র

রক্ত আমাশয় রোগের নূতন চিকিৎসায় ঔষধের পরীক্ষা

সেফ-ট্রায়াক্সন ইঞ্জেকশন

বাংলাদেশে শিগেলা জীবাণুজনিত রক্ত আমাশয় একটি প্রধান সমস্যা। গত কয়েক বছরে এই রোগের চিকিৎসায় অ্যামপিসিলিন সহ অন্যান্য এন্টিবায়োটিকের কার্যকারিতা হ্রাস পাইয়াছে। আমরা এই গবেষণায় সেফ ট্রায়াক্সন নামে একটি নূতন এন্টিবায়োটিক ব্যবহার করবো। বিদেশে এই ঔষধ ব্যবহার করে শিগেলা সহ অন্যান্য রোগ জীবাণুতে বেশ ভাল ফল পাওয়া গিয়াছে। এবং এই ঔষধ ব্যবহারে শরীরে কোন বিরূপ প্রতিক্রিয়া হয় না। আপনার যদি আমাশয় রোগ হয়ে থাকে তবে আপনাকে আমরা এই হাসপাতালে ভর্তি করে নেবো এবং আপনাকে অ্যামপিসিন ৪ গ্রাম অথবা সেফ ট্রায়াক্সন ১ গ্রাম ইনজেকশন দিব। (শিরায়) এর পর আপনাকে ৭ দিন হাসপাতালে থাকতে হবে। এবং প্রত্যহ দুইবার আপনার পায়খানা পরীক্ষা করা হবে। এতে বোঝা যাবে কত তাড়াতাড়ি আপনার অন্ত্র জীবাণু মুক্ত হয়। এ ছাড়াও পরীক্ষার জন্য সামান্য রক্ত (একবার) (১ সি সি) নেওয়া হবে। সাধারণ রোগ চিকিৎসার জন্যও এই পরিমান রক্তের প্রয়োজন হতো।

আপনি যদি এই গবেষণায় অংশগ্রহণ করতে না চান অথবা গবেষণা চলা কালে গবেষণা পরিত্যাগ করতে চান তবুও আপনাকে এখানকার সাধারণ চিকিৎসা আপনাকে দেওয়া হবে।

আপনি রাজী থাকলে নীচে সই করুন।

(আমাকে এই বিষয় সম্পূর্ণ বুঝিয়ে বলা হয়েছে)

গবেষকের স্বাক্ষর

রোগীর স্বাক্ষর/টিপ সহি

তারিখ----------

CEFTRIAXONE STUDY

HISTORY SHEET

Patient Name :

Hosp. Number :

DRUG [ ]

Study Number : [ ][ ][ ]

Date of Admission: DAY [ ][ ] MON [ ][ ] YR. [ ][ ]

Age : [ ][ ] Weight [ ][ ][ ]

Duration of Diarrhoea: [ ][ ][ ]

No. of Loose motion: [ ][ ]
24 hour before admission

Description of Stool: [Loose] [Mucus] [Blood + Mucus]

Abdominal Pain : [NO] [YES] Malaise / NO / YES/

Fever : [NO] [YES] Headache / NO / YES/

Tenesmus : [NO] [YES] Rectal Prolapse [NO] [YES]

Medication outside : [NO] [YES]

Physical Examination

Pulse [ ][ ][ ] Resp. [ ][ ] Temp [ ][ ][ ]

Pallor [NO] [YES] Liver Palpable [NO] [YES] Splean Palpable [NO] [YES]

He [Normal] [Abnormal]

Lungs Rales [NO] [YES] CNS [Normal] [Abnormal]

CEFTRIAXONE STUDY

LABORATORY DATA SHEET

DRUG ☐

HOSPITAL NO.

STUDY NO.

Blood Date / / / /

Hct ☐☐ Poly ☐☐ Mono / /

TWBC ☐☐☐☐ Band ☐☐ Eosino / /

Serum Elect. Lympf ☐☐ Blood gr. /

ESR / /

Na ☐☐☐

K ☐☐☐

Cl ☐☐☐

CO_2 ☐☐☐

Creat ☐☐☐

Protein ☐☐☐

Serum Drug Conc.

☐☐

Urinalysis

☐ 1 Normal 2 Abnormal

CEFTIAXONE STUDY

DRUG ☐ CLINICAL DATA SHEET

HOSPITAL NO. STUDY NO.	0 Day		1ST		2ND		3RD		4TH		5TH		6TH		7TH	
No. of stool	8 A.M.	4 P.M.														
Blood + Mucus																
Mucus only																
Abdominal Pain																
Fever																
Tenesmus																
Rectal Prolapse																

CEFTRIAXONE STUDY

DRUG ☐ LABORATORY DATA SHEET

HOSPITAL NO.
STUDY NO.

Stool Physical Examination

	0 Day	1ST	2ND	3RD	4TH	5TH	6TH	7TH
Colour								
Consistancy								
pH								
Blood								
Mucus								
Pus Cell/HPF								
RBC/HPF								
Macrophage/HPF								
Protozoa Veg								
Protozoa Cyst.								
Ova AL AD Otlurg								
Rectal Swab Culture								