36

Attachment 1. Date 21-1-81

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr Iqbal Kabir
Application No. 81-002
Title of Study Effect of Mecillinam in the treatment of Shigellosis

Trainee Investigator (if any) _____
Supporting Agency (if Non-ICDDR,B) _____
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 NA
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:
   ___ 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.

Kabir
Principal Investigator

Trainee

81-002
recd 22/1/81

SECTION I - RESEARCH PROTOCOL

(1) Title: Effect of Mecillinam in the Treatment of Shigellosis.

(2) Principal Investigator: Dr. A.K.M. Iqbal Kabir.

Co-Investigator: Dr. Syed Masud Ahmed, Dr. M.M. Rahaman, Mrs. S. Qudsia Akhtar.

(3) Starting Date: 1.2.1981.

(4) Completion Date: 29.2.1982.

(5) Total Direct Cost: $ 21897.

(6) Scientific Program Head:

This protocol has been approved by the Pathogenesis & Therapy working group.

Signature of Scientific Program Head: WB

Date: 16.1.81

(7) Abstract Summary: Mecillinam a member of new group of B-Lactam antibiotic, the amidinopenicillanic acid has a high activity against most members of enterobacteriaceae including E. coli Salmonella, Shigella, Proteus and Klebsiella.

We propose to investigate the efficacy of mecillinam in the treatment of Shigellosis. This will be done as a comparative trial involving 100 hospitalised adult patients. Of them 50 will be assigned to treatment with mecillinam and another 50 with ampicillin.

(8) Reviews:

(a) Ethical Review Committee: _____

(b) Research Review Committee: _____

(c) Director: _____

(d) BMRC: _____

(e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objectives:

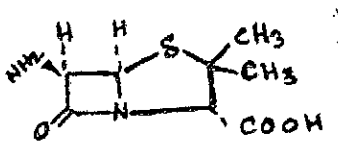
   a) To evaluate the efficacy of mecillinam in the treatment of Shigellosis.

   b) To compare the effect of mecillinam and ampicillin in the treatment of Shigellosis.

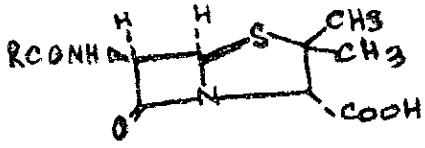
2. Background: Mecillinam a group of new antibiotic has extensive antibacterial effect against most of the gram negative bacteria including Shigella, Salmonella, E.coli, Klebsiella proteus etc.[1] Various studies in animal and human subjects show that it has quite low toxicity and been well tolerated[2]. But the drug has never been tried to see the efficacy in Shigellosis. Our study is designed to see the effect of mecillinam in the treatment of Shigellosis in Bangladeshi patients.

   Shigellosis is a world wide problem specially in developing countries. And multiple antibiotic resistance pattern in its various strains caused great concern to find out a suitable antibiotic for its treatment. Mecillinam could be an ideal solution to it. In vitro studies have shown that mecillinam has quite good effect against Shigellosis. Harold C. Neu showed in 25 strains of Shigella minimum inhibitory concentration with mecillinam (MIC value) was 0.4-50 µg/ml (Mean 0.8 µg/ml) whereas with ampicillin MIC value was 1.6-400 µg/ml (Mean 50 µg/ml)[3]. Another study (Godtfredson, 1977) showed inhibitory conc. with mecillinam in Shigellosis was 0.050 µg/ml whereas with ampicillin this was 1.0 µg/ml.

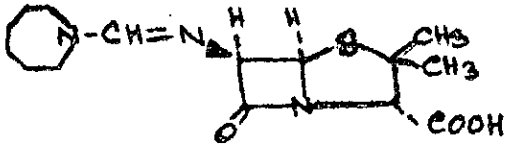
   Chemical structure. Mecillinam is a new group of 6 APA (amino-penicillanic Acid) derivative, which does not contain this amino group but instead contains a substituted amidino group in the 6 position. These are antibacterially active and had a very unusual antibacterial properties than that of other penicillins[4]. Chemical structures of 6-APA, Penicillin, mecillinam, and pivmecillinam are given below to have a clear idea.



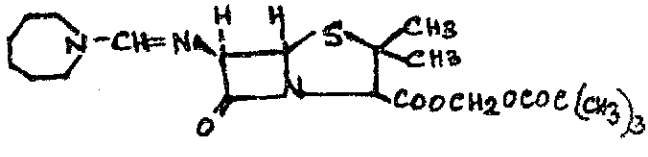
6-Aminopenicillanic acid



Penicillin



Mecillinam (FL 1060)



Pivmecillinam (FL 1039)

Mode of action of Mecillinam: When Land and Tybring first described the properties of mecillinam in 1972, they found the antibacterial activity is different from that of other known B-lactum antibiotics. If differs in two main respects:

1. Mecillinam is highly active against gram negative bacteria but had much reduced activities against gram positive bacteria. Whereas penicillins and cephalosporins cause the reverse[6].

2. Mecillinam produced different microscopical changes in the culture of E.coli from that of penicillins and cephalosporins. Morphological, biochemical and genetic studies have shown that penicillin binding protein 2 (PBP-2) of Each.coli is the target to which mecillinam interacts to result in the production of osmotically stable round cells. Detailed studies on the response of E.coli to mecillinam have shown that cell division is not inhibited for at least 45 minutes at 37°C. After this period cell mass continues increasing but the rate of cell division slows and finally ceases, then the cells become converted into ovoid and then large osmoticall stable round cell. After several hours of active growth in the presence of mecillinam these round cells lyse (7,8,9).

Route of Administration: Mecillinam is not absorbed by the oral route. So pivoloyal oxymethyl ester of mecillinam i.e. piv mecillinan been synthesised as orally active derivative. This is well absorbed from the gastro intestinal tract and during or after absorption is rapidly hydrolysed with the liberation of antibacterially active compound, mecillinam. The hydrolysis is catalysed by enzymes present in the blood and many tissue including intestinal mucosa[9].

Dose: Different studies showed that the effective dose of pivmecillinam 400 mg as capsule or tablet, which gave peak concentration C_{max} 5.2 $\pm$ 1.0/µg/ml and time for onset of peak T_{max} (h) - 0.89 $\pm$ 0.14[9].

Toxic effect: Both in acute and long term studies in animals and human mecillinam and piv mecillinam have shown a low degree of toxicities in comparison to penicillin and both compounds found to have no teratogenic effect.

3. Rationale: Shigellosis continues to be a major problem and causing mortality and morbidity among the population of the developing and under developed countries. Major emphasis had been given to this world-wide problem and several kinds of antibacterial agents been produced so far. But the multiple antibiotic resistance pattern of Shigella strains producing much concern to find out a new group of suitable antibiotic for the treatment of Shigellosis. In a study Mutanda et al[10] found Shigella flexneri in Bangladesh population being resistant to most of the known antibacterial agents. (Tetra. 84%, Ampicillin 6%, Chloromycetin 3%, Kanamycin 1%).

   The picture is really worrisome. There is need to investigate and evaluate antibacterial effectiveness with other new groups of antibiotics since not much research have been done in the treatment of Shigellosis especially in our country. It may be worthwhile to further investigate and evaluate the efficacy of mecillinam to treat Shigellosis.

B. SPECIFIC AIMS

1. The aim is to see the effect of mecillinam in the treatment of Shigellosis.

2. To compare the efficacy of mecillinam and ampicillin in the treatment of Shigellosis.

C. METHODS & MATERIALS

One hundred adult patients who attend the out-patient department of ICDDR,B with history of passing blood + mucoid stool but no history of taking medicine (antibiotic) outside would be included in this study. Stool microscopy shall be done from OPD and patients having considerable amount of pus cell, RBC, macrophage will be admitted to the study wards. Patients having other complicating organic diseases will be excluded.

The patients will be randomly assigned in a comparative clinical trial, into one of the two groups, one getting mecillinam (pivmecillinam) and other getting ampicillin which has been known as the drug of choice, as control. A total of 50 patients will be assigned to each group. Clinical examination will be done by study physician on admission. Daily records for clinical assessment will be done by history.

Clinical data sheet will be maintained according to the following criteria.

1. Number of loose motion (Frequency)
2. Blood + mucus in stool
3. Mucus only
4. Abdominal pain
5. Tenesmus
6. Fever
7. Rectal Prolapse

Admission data on

1. Stool Microscopy
2. R/S culture (all plates)
3. Serum Electrolyte
4. CBC
5. Urine Analysis for presence as excreta
6. Serum level.

Stool Microscopy will be done daily and for subsequent 6 days and follow up 15 day later.

Rectal Swab for subsequent 6 days will be done daily and follow up 15 day later.

Culture and sensitively will be done in all positive culture. CBC will be done on date of Admission, on date of Discharge and patients will be discharged on 7th day and or after full cure. Treatment for intestinal ova and parasite will be given on discharge.

D. SIGNIFICANCE

The idea is to find out a new group of antibiotic where multiple antibiotic resistance in Shigellosis causing a great concern. And mecillinam may be a suitable one.

E. FACILITIES REQUIRED

1. Office space: The present study room for research physician can be utilised.

2. Laboratory space: ICDDR,B existing laboratory

3. Logistic support: Data Processing and Computer support from the Statistics Branch may be needed.

F. COLLABORATIVE ARRANGEMENT

Leo Pharmaceuticals.

G. Data Analysis:

Assessments will be done clinically by

1. Frequency (Number of loose motion)

2. Disappearance of Blood from the stool

3. Disappearance of the mucus from stool

4. Absence of Abdominal pain

5. Absence of Tenesmus

6. Absence of fever

Laboratory Data Analysis:

1. Disappearance of pus cell, RBC, Macrophase from the stool microscopy.

2. Absence of positive stool culture

3. Absence of positive Rectal Swab culture

4. CBC Falling down the total white cell count

ABSTRACT SUMMARY

Mecillinam - a member of new group of B-Lactam antibiotic, the amidinopenicillanic acid has a high activity against most members of enterobacteriaceae including E. coli, Salmonella, Shigella, Proteus, Klebsiella.

We propose to investigate the efficacy of mecillinam in the treatment of Shigellosis. This will be done as a comparative trial involving 100 hospitalised adult patients. Of then 50 will be assigned to treatment with mecillinam and another 50 with ampicillin.

1. The population to be studied includes adult patients suffering from blood dysentery and the effect of Mecillinam will be seen in the treatment of Shigellosis.

2. Risks from the study is minimal and the drug has been used in European Population for other Gram Negative bacterial infection. Minor side effects include Nausea, vomiting. There will be no physical, social or psychological risks to the patient.

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 thumbimpression) will be obtained from all patients before entry into 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 the history of illness and is needed only for clinical management of the disease. Five minutes will be enough to take such a clinical history.

7. The individual will gain through treatment of his illness and may possibly benefit from the therapeutic effect of the drug more quickly. Soceity will gain if a suitable new drug can be found for shigellosis where multiple antibiotic resistance is frequently encountered.

8. The study will require examination of stool, blood and urine.

BIBLIOGRAPHY

1. Godtfredsen, W.O. An Introduction to Mecillinam. Journal of Antimicrobial Chemotherapy (1977) 3 Supp B.1-4.

2. Godtfredsen, W.O. An Introduction to Mecillinam, J. Anti Microb. Chem (1977)3 Supp B 1-4.

3. Neu N.C. Mecillinam, A Novel Penicellavic Acid Derivative with Unusual Actively Against Gram Negetive Bacteria.

4. Land, F and Tybring L. 6B. Amidino Penicillanic Acid, a new group of antibiotic. Nature New Biology 236: 135-7 (1972).

5. Spratt, B.G. Distinct Penicillin binding proteins involved in the division, elongation, and shape of Esch. coli. Proceedings of National Academy of Science of the U.S.A. 72: 2999-3003 (1975).

6. Spratt, B.G. A composition of the binding properties of two 6-B-amidinopenicillinic acid derivatives which differs in their physiological effects on Esch. coli. J. Antimicrobial Agents & Chemotherapy 11:161-6 (1977a).

7. Tybring, L & Melchoir, N.H: Mecillinam (FL1060), a 6B amidinopenicillanic acid derivatives: bacteriocidal action and energy in Vitro. Antimicrobial Agents and Chemotherapy 8:271-6 (1975).

8. Andrew, J., Kendall, M.J. & Mitchard, M. Factors influencing the absorption and disposition of mecillinam and pivmecillinam in man. British Journal of Clinical Pharmacology 3:627 (1976).

9. Roholt, K. Pharmacotinetics: Studies with mecillinam and pivmecillinam. J. of Antimicrobial Chemotherapy (1977), 3 (suppl B), 71-81.

10. Mutanda, L.N. Antibiotic-Resistance and Pattern of Shigella flexneri Serotypes in Dacca. Bangladesh Medical Journal 9:1-7. 1980.

SECTION III - BUDGET

A. DETAILED BUDGET

1. PERSONNEL SERVICES

Name	Position	% of effort	Annual salary	Project Requirement Taka	Dollars
Dr. Iqubal Kabir	Principal Investigator	75%	Tk. 54,139	40,605	
Dr. M.M. Rahaman	Co-Investigator	1%	$ 23,520	-	235
Ms. S.Q. Akhtar	"	5%	Tk. 46,800	2,340	
Dr. S.M. Ahmad		50%	Tk. 46,877	23,439	
Field Asst. (Follow up)		25%	Tk. 25,077	6,269	-
Study Nurse	"	100%	Tk. 28,728	28,728	
			Tk.	101,381	235

2. SUPPLIES AND MATERIALS:

1. Mecillinam to be supplied by LEO Pharmaceuticals
   No Cost to ICDDR,B
2. Cap Ampicillin - 2000 Nos. Tk. 10,000
3. Misc. Vermox tablet, Multivitamin tablet, Fersolate, Flagyl 15,000

Laboratory Test	No. of Test		Cost/Test	Tk.	Dollar
1) CBC	200	Tk.	4.20	840	-
2) Blood Electrolytes	100		3.90	390	
3) Stool Microscopy	700		2.05	1,435	-
4) Rectal swab culture	1,400		7.25	10,150	-
5) Blood for serum level of drug	100		30.00	3.000	-
6) Urine Analysis	100		2.35	235	-
			Total Tk.	16,050	

B. EQUIPMENT None

C. PATIENT HOSPITALIZATION: Tk. 150 per day/patient

Sub total Tk. 150,000

D. O.P.D. CARE: None

E. ICDDR,B TRANSPORT 30 miles x 100 x 3 Tk. 9,000

F. TRAVEL AND TRANSPORTATION: Tk. 20 x 100 Tk. 2,000

G. TRAVEL AND TRANSPORTATION OF THINGS None

H. RENT AND COMMUNICATION:

I. PRINTING AND REPRODUCTION 15,000 $ 300

J. CONSTRUCTION: None

K. OTHERS: None

BUDGET SUMMARY

1.	Personnel	Tk. 1,01,381	$ 235
2.	Supplies & Material	Tk. 25,000	
3.	Equipments - None		
4.	Hospitalization	Tk. 150,000	
5.	Laboratory test -	Tk. 16,050	
6.	Out Patient None		
7.	ICDDR,B Transport	Tk. 9,000	
8.	Transportation of things	Tk. 2,000	
9.	Rent/Communication - None		
10.	Printing/Reproduction	Tk. 15,000	$ 300
11.	Contractual services	None	
12.	Construction	None	
13.	Follow up patient care Taka 20/day	Tk. 2,000	
	GRAND TOTAL	3,20,431	$ 535

INTERNATIONAL CENTRE FOR DIARRHOEL DISEASE
RESEARCH, DAGCA

MECILLINAM STUDY

(CONSENT FORM)

ICDDR,B has been trying to develop advanced methods of treatment of shigella dysentery. In this research we shall use a new antibiotic, Mecillinam which has got no adverse reaction in the body. Various studies done in other countries has shown good result using this drug in shigellosis.

You will have to stay for 7 days in hospital after admission. During this time 6 cc. of blood will be taken from you for the determination of serum electrolyte and CBC. This same amount of blood would have been taken even in case of general treatment. Except this rectal swab for culture will be taken twice daily. This test will show whether you have become free from shigella bacteria. Fifteen days after complete cure and discharge from the hospital we shall bring back you by our own cost and effort and examine your stool to determine whether you are suffering from some disease. At that time you will be given Tk. 20 for your transport and other expenses.

You will have complete freedom to drop yourself from the study anytime you like. The regular will not be refused and you will not be penalised in any way whether you participate or not.

Your co-operation will be highly appreciated. If you agree please sign.

Signature of Investigator

Signature of the patient
Thumb impression

"বাংলাদেশ আন্তর্জাতিক উদরাময় গবেষনা কেন্দ্র"

"সম্মতি পত্র"

বাংলাদেশ আন্তর্জাতিক উদরাময় গবেষনা কেন্দ্র লীলেনা জীবানুজনিত রক্তআমাশয় রোগের উন্নততর চিকিৎসার উদ্ভাবনের জন্য চেষ্টা চালিয়ে যাচ্ছে। আমরা এই গবেষনায় "সেফিক্সিমনাম" নামে একটি এন্টিবায়োটিক ব্যবহার করব। এই ঔষধ ব্যবহারে শরীরে কোন বিরূপ প্রতিক্রিয়া হয় না। বিদেশে এই ঔষধ ব্যবহার করে রক্তআমাশয়-এর চিকিৎসার বেশ ভাল ফল পাওয়া গেছে।

ভর্তির পর আপনাকে ৭দিন হাসপাতালে থাকতে হবে। এই সময়ে আপনার রক্তে ইলেকট্রোলাইট এবং শ্বেত কনিকার সঠিক পরিমাপের জন্য আপনার শরীর থেকে প্রথমোটে ৬ মিঃ মিঃ রক্ত নেওয়া হবে। আপনার সার্বিক চিকিৎসার জন্যও এই পরিমান রক্তের প্রয়োজন হত। এ ছাড়াও প্রতিদিন ২বার রেক্টাল সোয়াব নেয়া হবে। এই পরীক্ষায় বোঝা যাবে কত তাড়াতাড়ি আপনার অন্ত্র জীবানুমুক্ত হয়। আপনি সম্পূর্নভাবে রোগমুক্ত হবার পর ১৫ দিন পরে আমরা নিজ খরচায় আপনাকে হাসপাতালে নিয়ে আসব এবং আপনার পায়খানা পরীক্ষা করব। আপনার যাতায়াত এবং আনুসংগিক খরচের জন্য আপনাকে কিছু টাকা দেয়া হবে।

আপনি এই গবেষনায় অংশগ্রহন না করতে চাইলেও আপনার স্বাভাবিক চিকিৎসার কোন ত্রুটি হবে না। গবেষনাচলাকালীন যে কোন সময়ে আপনি চাইলে গবেষনা পরিত্যাগ করতে পারেন।

আপনার সহযোগিতা আমাদের কাম্য। আপনি রাজী থাকলে নীচে সই করুন।

গবেষক

রোগীর স্বাক্ষর/টিপসহি

HISTORY SHEET

Patient Name :

DRUG

Hosp. Number :

Study Number :

Date of Admission: DAY MON YR.

Age :

Weight

Duration of Diarrhoea:

No. of Loose motion:

Description of Stool: Loose | Mucus | Blood + Mucus

Abdominal Pain : NO | YES

Fever : 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

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																

(17)

LABORATORY DATA SHEET

DRUG [ ]

HOSPITAL NO.

STUDY NO.

Blood

Hct [ ][ ]

TWBC [ ][ ][ ][ ]

Poly [ ][ ]

Band [ ][ ]

Lympf [ ][ ]

Serum Elect.

Na [ ][ ][ ]

K [ ][ ][ ]

Cl [ ][ ][ ]

CO_2 [ ][ ][ ]

Creat [ ][ ][ ]

Serum Drug Conc.

[ ][ ]

Urinalysis

[ ] 1 Normal 2 Abnormal

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								