Attachment 1.

Date 23 January 1985

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator P. Speelman

Trainee Investigator (if any) 9

Application No. 83-007

Supporting Agency (if Non-ICDDR,B)

Title of Study

Loperamide in Travellers' Diarrhea.

Project status:
(X) 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).

Source of Population:
(a) Ill subjects (Yes) No
(b) Non-ill subjects Yes (No)
(c) Minors or persons under guardianship Yes (No)

Does the study involve:
(a) Physical risks to the subjects Yes (No)
(b) Social Risks Yes (No)
(c) Psychological risks to subjects Yes (No)
(d) Discomfort to subjects Yes (No)
(e) Invasion of privacy Yes (No)
(f) Disclosure of information damaging to subject or others Yes (No)

Does the study involve:
(a) Use of records, (hospital, medical, death, birth or other) (Yes) No
(b) Use of fetal tissue or abortus Yes (No)
(c) Use of ~~organs or body fluids~~ (Stool Specimen) (Yes) No

Are subjects clearly informed about:
(a) Nature and purposes of study (Yes) No.
(b) Procedures to be followed including alternatives used Yes (No)
(c) Physical risks Yes (No)
(d) Sensitive questions Yes (No)
(e) Benefits to be derived (Yes) No
(f) Right to refuse to participate or to withdraw from study (Yes) No
(g) Confidential handling of data (Yes) No
(h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure N.A. 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 N.A
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:
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.

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

Principal Investigator

Trainee

83-007

10/29/83

SECTION 1 - RESEARCH PROTOCOL

1. TITLE: LOPERAMIDE IN TRAVELLERS' DIARRHEA

2. PRINCIPAL INVESTIGATOR: Dr. P. Speelman

   CO-INVESTIGATORS: Dr. M. J. Struelens, Dr. D. Patte and Dr. T. C. Butler

3. STARTING DATE: March 1, 1983

4. COMPLETION DATE: March 1, 1984

5. TOTAL INCREMENTAL COST: US $ 4100.00

6. SCIENTIFIC PROGRAMME HEAD: This protocol has been approved by the Pathogenesis and Therapy Working Group.

Signature of Scientific Programme Head: [signature]

Date: [illegible] 1, 1983

7. ABSTRACT SUMMARY:

Annually more than 100 million travellers suffer from diarrhea. Concern over diarrheal illness has led the traveller to a variety of treatments. The opiates have been used for long time in the treatment of diarrhea. Two synthetic narcotic analogues, diphenoxylate and loperamide are frequently used by travellers with diarrhea. However, many doctors discourage the use of these drugs for a variety of reasons. New data about loperamide suggest an important antisecretory action of this drug. These data, together with the fact that many travellers with diarrhea treat themselves with synthetic opiates are the rationale for this study. We plan to study the efficacy and safety of loperamide for treatment of travellers' diarrhea in a randomized double-blind, placebo controlled trial. In each group 40 patients will be studied.

8. REVIEWS:

(a) Research involving human subjects: _____

(b) Research Committee: _____

(c) Director: _____

(d) BMRC: _____

(e) Controller/Administrator: _____

SECTION 11 - RESEARCH PLAN

A. INTRODUCTION:

1. Objectives:

To study the efficacy and safety of loperamide in the treatment of travellers' diarrhea.

2. Background:

Annually more than 250 million people travel from one country to another, and tourism has become economically important, especially in developing countries. With an attack rate of 25-50% diarrheal illness may affect more than 100 million of these visitors yearly; 30% will be ill enough to be confined to bed and another 40% will have to alter their scheduled activities[1]. Concern over diarrheal illness has led the traveller to a variety of treatments. For centuries, various starches talcs, chalks, gums, absorbants, plant roots etc etc have been used for travellers' diarrhea. Combinations of Kaolin, Pectin and Aluminium are frequently used but evidence that these drugs diminish intestinal fluid loss is lacking.

Nowadays, most authorities in this field agree that antimicrobial drugs for prophylaxis of travellers' diarrhea should not be used in routine travel.

Dupont has recently shown that early treatment with trimethoprim-sulfamethoxazol or trimethoprim alone is a good alternative to prophylatic use of drugs for travellers' diarrhea[2]. However, complications of using antimicrobial drugs, as development of resistance of gut flora, skin rash, antibiotic associated colitis and Stevens-Johnson syndrome and ineffectiveness in preventing infections, like e.g. Campylobacter jejuni limit the value of this regimen.

The opiates have been used for long time in the treatment of diarrhea. Two synthetic narcotic analogues, diphenoxylate and loperamide have been introduced recently. These opiate drugs are thought to exert their benefit by reducing propulsive motility. However, they have also been found to inhibit fluid secretion in animal models of diarrhea. A single report[3] involving a shigella vaccine, in which infected volunteers treated with this drug had enhanced symptoms and prolonged fecal excretion of the shigella organism has led many workers in this field to discourage the use of these types of drugs, despite the fact that many people never travel without diphenoxylate or loperamide in their suitcase and go on doing so.

Considering the possible complications of antimicrobial drugs and the new data about the antisecretory action of loperamide, it seems justified to explore the efficacy and safety of loperamide in the treatment of travellers' diarrhea.

Drug information:

Loperamide, like diphenoxylate is a piperidine derative:

4 - (P - chlorophenyl) - 4 - hydroxy - N,N - dimethyl - alfa, alfa - diphenyl - 1 - piperidine - butyramide (4).

The first synthetic antidiarrheal diphenoxylate was discovered in 1956. Diphenoxylate is chemically related to pethidine and like pethidine diphenoxylate produces characteristic opiate-like effects. While diphenoxylate constitutes a major improvement over the opium-derivatives, overdosage produces opiate-like central effects.

In 1969 loperamide was synthetized. This drug was found to be more potent than diphenoxylate and to be essentially free of opiate-like CNS-effects. During the period '74-'78 the drug was extensively studied clinically and it was found to improve the consistency of stools and to reduce the frequency of stools without the central action of narcotics. Loperamide has a high affinity for receptors along the small intestine, where it acts at low concentrations. Small amounts only may pass the gastrointestinal barrier and reach the systemic circulation.

For a long period opiate drugs were thought to exert their action by reducing propulsive motility. However, recently new data have shown an important antisecretory effect of loperamide in addition to the effect on the smooth muscle action of the gut. Mc Kay has demonstrated that morphine and enkephalin analogues stimulate chloride absorption, possibly by means of a Cl/HCO_3 exchange (5). Sandhu has shown (in animal studies)

that loperamide reverses prostaglandin E_2 and cholera toxin-induced secretion[5]. This antisecretory effect is blocked by naloxone, suggesting an effect on opiate receptors. Hardcastle et al found that the primary action of loperamide is to abolish the inhibition of Na^+-absorption induced by prostaglandings (5).

Side effects of loperamide are rare but have been reported: constipation, nausea, abdominal pain, dizziness, rash and a dry mouth. Several of these complaints may however be due to the diarrheal disease to.

Rationale:

New data about loperamide suggest an important antisecretory effect of the drug. Since many years lots of patients use opiates to treat themselves for diarrhea. This study will demonstrate whether we should encourage or discourage this practice.

Specific aim:

To answer the question, whether loperamide is an effective and safe drug for treatment of travellers' diarrhea.

Methods of procedure:

A. Patient selection. (2 groups of 40 patients)

Patients have to fulfil the following criteria for admission into the study:

1. Age older than 16 years
2. Onset of diarrhea less than 72 hours ago
3. $\geq$ 3 unformed stools/24 hours
4. Availability for follow-up study during 5 more days.
5. Given written informed consent.
6. Stool ME result: no trophozoites of E. histolytica.
7. No prior drug intake
8. No high fever ($>39^{\circ}C$).
9. No visible blood in the stool
10. Not pregnant.
11. No history of severe constipation.

B. Procedure:

1. The study nurse explains the study to the patient.
2. She records the medical history and performs a limited physical examination, using a standard form (appendix).
3. She obtains a fresh stool specimen for microscopic examination and culture for:
   - Salmonellae sp.
   - Shigella sp.
   - Vibrio's
   - ETEC
   - Campylobacter jejuni
   - Aeromonas hydrophila
   - Plesiomonas shigelloides

4. She gives the capsules to the patient and explains the dosage-schedule, the diarrhea-diary and schedules appointments for return to the clinic at day 3 and 5 after start treatment.

C. Drugs and randomization:

Active drug and placebo will be supplied by Janssen Pharmaceutica. A randomization list will be made and the code for active drug and placebo will be kept in the Director's Office. Study number and treatment number will be the same.

D. Dosage-schedule:

Patients will take 2 capsules in the presence of the study nurse. Patients will be adviced to take 1 capsule after every bowel movement of unformed stool with a maximum of 8 capsules per day. As soon as the stool consistency is semiformed or formed the patient has to discontinue therapy.

E. Follow-up:

Patients will be requested to fill out a diarrhea diary (appendix) and will be asked to return to the clinic at day 3 and 5 after start of therapy to check the progress and/or side-effects.

F. Data-analysis:

Both groups will be compared using Chi-square methods and Student "t" test for:

- No. of bowel movements\per day
- Total no. of bowel movements during study period.
- Duration of presence of liquid/loose stools.
- Duration of abdominal cramps/distention.
- Duration of nausea
- Duration of vomiting
- Presence of side-effects.

Significance:

Positive results from this study may lead to a trial of this drug for treatment of severe watery diarrheas as cholera and ETEC (LT).

Facilities required:

1. Office and laboratory speace is already provided.
2. The study will be performed in the Travellers' Clinic
3. No hospital admissions
4. Animal resources are required for ETEC testing.
5. A special study nurse will be hired.
6. No major items of equipment are required.
7. The study requires support of the microbiology and clinical pathology. laboratory.

Collaborative arrangements: None

P.S.

After discussion in the PTWG the following items have been included in the protocol.

- We will ask the patients to return all unused pills, so that supposed pill intake can be matched with the number of stools recorded in the patients' diary (without patients' khowledge), to check on accurary of recording and drug compliance.
- Patients, returning to the clinic on day 3 and 5 of the study have to Provide stool specimen on these days to check the consistency and to reculture the stool.
- We will request the involved laboratory to use the Biken-test for E. coli L.T -detection.

REFERENCES

1. S. L. Gorbach. Travelers' Diarrhea; Editorial Lancet. Lancet 307 (14); 881, 1982.

2. DuPont HL, Reves R.R., Galind. E., et al. Treatment of Travelers' Diarrhea with Trimethoprim/Sulfamethoxazole and with Trimethoprim alone. Lancet 307 (14), 841-844, 1982.

3. DuPont H.L., Hornick R.B. Adverse effect of Lomotil therapy in shigellosis. JAMA 226: 1525-1528, 1973.

4. Goodman and Gilman's: "The Pharmacological Basis of therapeutics" Sixth edition, 1980. Macmillan Publishing Co. Inc. New York.

5. Clinical Research Reviews: Diarrhoea: new insights. Volume 1, Supplement 1, 1981. Edited by N.W. Read.

SECTION III - BUDGET
(incremental costs)

1. Personnel services (1 year)	% effort	US Dollar
Dr. P. Speelman Dr. M. Struelens Dr. D. Patte Dr. T. C. Butler	Continuation of existing travellers' clinic services (no incremental costs)	
Study nurse (local salary scale)	100	1500
Techn. Clinical Pathology	20	900
Techn. Microbiology	20	
Techn. Animal House	20	
	Sub Total=	2400
2. Supplies and Materials:		
Laboratory media, reagents		350
Laboratory tests - Stool M.E. 450 X Tk. 5 - Stool culture 450 X Tk.30		650
	Sub Total =	1000
3. Equipment		Nil
4. Patient hospitalization		Nil
5. Outpatients care		Nil
6. ICDDR,B transport (for follow-up patients, if necessary)		Nil Sub Total= 200
7. Travel and Transportation		Nil
8. Transportation of things		Nil
9. Rent/Utilities		Nil
10. Printing/Xerox		Sub Total = 500
11. Other contractual services		Nil
12. Construction/Renovation		Nil
GRAND TOTAL	= US DOLLAR	4100

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. 80 expatriate patients, older than 16 years, with an onset of diarrhea less than 72 hours ago will be selected for the study. Patients with a "complicated" diarrhea (high fever, visible blood in stool, amebae in stool) are excluded. Pregnant women and patients with a history of constipation are also excluded.

2. Travellers' diarrhea is usually a self limited disease. Many patients already use loperamide for travellers diarrhea without severe side effects reported. Some patients with specific cause of travellers' diarrhea (e.g. G. lamblia) have to wait 5 days for specific treatment. Patient with severe episodes of shigellosis and amebiasis have been excluded from study by the admission criteria.

3. Daily follow-up at the Traveller's Clinic or by telephone will minimize potential risks.

4. All records will be kept confidential in a locked filing cabinet in the Travellers' Clinic.

5. Informed consent will be obtained.

6. Interview questionaire will be short and not take more than few minutes (see appendix).

7. This study will hopefully answer the question if doctors should encourage or discourage the use of synthetic opiates in acute diarrhea.

8. The study will require stool only.

Note:

I want to perform this study in our travellers' clinic with expatriate patients to answer the question whether synthetic opiates, frequently used by travellers, are really useful or not. Loperamide seems to be the most potent synthetic opiate. I did not get any request now or in previous days, from the Janssen Company to perform such a study. Dr. Molla received a request to try Loperamide in Bangladeshi patients a few years ago, but refused. I wrote a letter in December, 1982 to request Janssen to supply me with active drugs and placebo. No answer has been received till date. No request for financial support has been made.

CONSENT FORM

ICDDR,B is an international centre for research on diarrheal disease. We invite you to participate in the following study. You probably know that synthetic opiates (Lomotil, Imodium) are frequently used by patients with diarrhea. For a variety of reasons many doctors discourage the use of these drugs. In this study we will try to answer the question whether Loperamide (Imodium) is an effective and safe drug for treatment of travellers' diarrhea. Eighty adult, non-pregnant patients with diarrhea (onset less than 72 hours ago and no drug intake) will be treated with Loperamide (Imodium) capsules or placebo capsules in a double blind study. (Doctor and patient do not know who gets the placebo or the active drug). The study lasts 5 days. On day 1, 3 and 5 you have to come to our clinic to bring a stool sample and to check the diarrhea diary (attached), which you have to fill out. On day 2 and 4 you will receive a phone-call from our nurse. In case you have got the placebo capsules and a specific cause for the diarrhea is found (that may take 2-3 days), you will get the specific treatment on day 5. Loperamide capsules are available all over the world since about 7 years. Some side-effects have been reported; the most common side-effect is constipation. In general it has been proven to be a safe drug.

If you participate in this study we will treat you free of charge for this diarrheal episode.

If you decide to participate, please sign here.

Patient: _____

Date: _____ Doctor or Nurse: _____