28 Date 8/11/83

ETHICAL REVIEW COMMITTEE, ICDDR,B. 30/11/78

cipal Investigator Dr. D. Patte

ication No. 83-043(P)

e of Study Antisecretory drug

rial: Clonidine Hydrochloride

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)

le 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)

oes 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

re 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
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.

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

SECTION 1 - RESEARCH PROTOCOL

(Limited study)

1. TITLE: ANTISECRETORY DRUG TRIAL: CLONIDINE HYDROCHLORIDE.

2. PRINCIPAL INVESTIGATOR: Dr. D. Patte

   CO-INVESTIGATORS: Dr. G.H. Rabbani, Physician Hosp.

3. STARTING DATE: 15th December, 1983

4. COMPLETION DATE: 15th March, 1984

5. TOTAL INCREMENTAL COST: US $ 1520.00

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

J Butler
Signature of Programme Head

Date: 28-11-83

7. ABSTRACT SUMMARY:

A limited study to investigate the antisecretory property of Clonidine Hydrochloride in severe cholera patients is planned. One group of 20 adult cholera patients of both sexes will be challenged with 0.9 mg of clonidine daily. A control group of 20 other patients selected according to the same criteria will receive no drug. After assessment of the basal purging rate over 6 hours and after adequate rehydration, the drug will be administered in two doses at an interval of 12 hours in the test group. Purging rate will be assessed 4 hourly, and electrolytes loss once in 24 hours in each group. After 3 days of treatment, results will be compared between the two groups. Pathophysiological aspects will be further studied if any effect is demonstrated.

8. REVIEWS:

(a) Ethical Review Committee: _____

(b) Research Review Committee: _____

(c) Director: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION:

1. Objectives:

To determine wether clonidine has any antisecretory effect in cholera. Clonidine hydrochloride has been listed by WHO (CDD program) as possible antisecretory drug to be tested in humans.

2. Background:

A series of drugs have shown antisecretory effect against cholera toxin induced fluid loss, either experimentaly or in humans. None of them specifically acts through the autonomic nervous system, though some of them, such a s chlorpromazine, have neurological effects. Such a pathophysiological aspect has, so far, scarcely been taken into account. However several instances of interactions between cholera toxin and adrenergic nerves have been demonstrated experimentaly. Some experiments show antagonist effects of cholera toxin on α mediated phenomenons such as norepinephrine induced vaso-constriction (16). In the gut, adrenaline is thought to increase the net uptake of sodium and chloride through an α mediated mechanism which has been demonstrated in vitro (2-7).

On the other hand, cholera toxin has shown some agonist effect on β mediated phenomenons such as the rate of the heart pace maker cells (19). In the gut cells, β receptors are scarce and a cholera toxin induced stimulation remains unlikely, meanwhile an α blockade (or α blockadelike) effect is possible. Therefore it becomes relevant to investigate the effect of α agonists as possible antisecretory drugs. This hypothesis has been partly tested (from another stand point) by T. Nakaki et al (15) in intestinal loops challenged with cholera toxin. They demonstrated that clonidine (an α_2 agonist) was 100 fold more potent than methoxamine (α_1 agonist) an even 3 fold more potent than adrenaline in inhibiting the cholera toxin induced fluid accumulation. Interestingly enough is the fact that the dramatic drop in fluid secretion in the clonidine treated loops is not correlated with any parallel drop in cAMP accumulation. This rises the question of the exact role of cyclic AMP in cholera secretion as a cause or a symptom.

Another argument comes from a case report by Mc Arthur et al (14). They successfully reduced the purging rate in a patients with lung cancer, of whom the tumor was found to contain very high level of VIP, with clonidine as well as with lidamide, which has some structrual similarities to clonidine. Clonidine was given at a dosage ranging from 0.2 mg to 0.6 mg daily with a clear dose related effect.

3. Clonidine hydrochloride:

(a) Pharmacology, metabolism:

Clonidine hydrochloride is an imidazoline derivative mainly used as antihypertensive agent. It stimulates α_2 adrenergic receptors but is, in fact a partial agonist. Its action is central and peripheral, resulting in:

- a decrease in the central sympathetic outflow
- and an inhibition of the neural release of epinephrine.

The central target of the drug is not precisely known. Experimental evidences suggest the nucleus tractus solitarius (5,8,9), a region of the lower brain stem rich in epinephrine/norepinephrine loaded neurons (4), as the main site. However sites in the spinal cord itself may be involved. At the peripheral level, the effect of clonidine on blood pressure can be inhibited by Yohimbine, a specific α_2 antagonist. This suggest a presynaptic α_2 mechanism (18), although some α_1 effect (postsynaptic) can not be excluded (20). The present study mainly relies on the peripheral effects.

The effect of clonidine depends on the bioavailability of the unchanged drug.

After a single oral dose in normal volunteers, the bioavailability averages 75% with an elimination half-life of 8.5 hours (3). 60% of the clearance is due to renal elimination in an unchanged form. The hypotensive effect in non-hypertensive subjects lasts for 8 hours (6).

) Effects on haemodynamics:

Clonidine acts mainly by relaxing the capacitance vessels and decreasing the total peripheral resistance. After single oral dose, the maximum effect is reached within 20 minutes and lasts for several hours. It includes a fall in:

- Pulmonary arterial pressure
- Cardiac output.
- Cerebral blood flow with increase in cerebral resistance (13)
- Renal vascular resistances with maintained blood flow (1).

Glomerular filtration is either unchanged or slightly decreased but in any case sodium excretion is sharply decreased as well as plasma renin activity (12, 17). The most important aspect of clonidine effects is the fact that it does not alter the reflexe control of haemodynamic regulation (11). Therefore, normal or near normal responses are observed to Valsalva maneuver, tilt test or excercise, and, in normal subjects, fall in blood pressure remains moderate with no or only slight orthostatic hypotension.

(c) Side effects and toxicity:

The most common side effects in man are:

- sedation which improves while therapy is continued.
- and dry mouth through a centrally mediated inhibition of salivation.

Orthostatic hypotension is rare and moderate and impotence may occur eccasionally in chronic treatment. It improves when drug is discontinued. Clonidine may enhance preexisting depressive states. In hypertensive patients chronically treated with sole clonidine, its sudden withdrawal can result in severe hypertensive crisis. Reinstitution of clonidine or B blockers usually control the crisis. No teratological effect has been so far demonstrated but the drug may have some embryo toxicity. The effects of clonidine on blood pressure is enhanced by diuretices, meanwhile tricyclic antidepressants and imipramine can nullify the effects of the drug. There is, otherwise, no demonstrated interaction with other drugs.

B. SPECIFIC AIMS:

Besides a possible therapeutic use of the drug to inhibit cholera secretion, the study also aims to seek evidences for a role of the autonomic nervous system in cholera secretion.

C. METHODS AND PROCEDURE:

1. Patients selection:

Patients will be elligible to join the study according to the following criteria:

- Adults, male or female
- Double checked positive dark field microscope examination and positive culture.
- Purging rate above 200 ml/h for at least 6 hours.
- No focal or systemic infection.
- No preexisting cardiovascular disease.
- No neurological finding
- Non-pregnant (last menses within the last 2 weeks)
- No previous treatment except ORS
- Informed written consent obtained.

2. Procedure:

Patients fulfilling the above criteria will be randomly assigned either to test group or control one (see below) upto a maximum of 20 patients in each group. They will be admitted to the study ward and will be kept on a NPO regimen for the first 24 hours. Appropriate diet will be given subsequently.

The following data will be recorded for 3 consecutive days:

- daily = Body weight
  Total input (oral and I.V.)
  Total output

- 4 hourly = Purging rate
  Consistency of stools.
  Urine flow
  Presence or absence of vomiting during the past 4 hours.
  Temperature
  Blood pressure
  Heart rate
  Input (oral and I.V.) during the past 4 hours.

- 30 min after drug administration: Blood pressure
  Heart rate

Every 24 hours, a sample of stool will be collected for:

- electrolyte
- TCO_2
- and pH analysis.

3. Drug administration

In hypertensive patients, therapeutical effect is achieved with doses ranging from 0.3 up to 1 mg depending on the type of hypertension and associate therapy. In patients treated only with clonidine, dosage averages 1mg daily although doses as high as 3mg daily have been used safely in some cases. The appropriate dosage for anti-secretory effect cannot be extrapolated from in vitro experiments neither from those in isolated intestinal loop.

Therefore, it has been decided to use the maximum average dose commonly used in hypertensive subject, which is demonstrated to be safe. The selected patients will be randomly assigned to the test group or to the control one.

Test Group:

Clonidine hydrochloride at our disposal comes into 0.150mg tablets. A total daily dose of 0.9 mg will be given to these patients in two doses of 3 tablets at 12 hours interval. To avoid orthostatic hypotension, drug will not be started until the patient is considered as normally hydrated, according to the standard clinical criteria, and demonstrates a good volume pulse.

Control group: rehydration and surveillance will be carried out in the same way as for test group, but not drug will be given.

4. Treatment and benefit to the patients:

All patients will be adequately rehydrated and maintained using only intravenous fluids during the first 24 hours of trial. Subsequently, I.V. fluid will be continued and standard diet with measured volumes of plain water will be allowed per oral according to their condition. Routine clinical and laboratory investigations will be performed whenever needed. After 3 days, patients will be either discharged or returned to the general ward or TC. When leaving the study ward they will be treated with a course of Tetracycline and those found to be infected with intestinal parasites will receive appropriate therapy.

SIGNIFICANCE:

The significance of the study will be to identify clonidine hydrochloride as a potentital antisecretory agent in cholera patients. Considering the mechanism of action of this drug it may also cast a new light on pathophysiology. If any effect is demonstrated, it will be further studied in both aspects.

Data analysis = data will be analysed in the following guidelines:

- Clinical comparability of the patients in the two groups: age, duration of illness before therapy and initial purging rate.

- Comparison of stool volume over the study

- Comparison of stool content in electrolytes in each group at a given time.

- Relationship between purging rate and rate of inhibition of fluid loss in each group.

E. FACILITIES REQUIRED:

1.	Office space:	Present facilities will be utilized.
2.	Laboratory space:	No extra lab space is required. Existing laboratories will be utilized.
3.	Hospital resource:	40 adult patients will be studied in the study ward for 3 days.
4.	Animal resources:	None
5.	Logistic support:	Data processing and computer support are required from Statistical and Computer Branches.
6.	Major equipment:	None
7.	Others:	None
8.	Transport:	None

F. COLLABORATING ARRANGEMENT:

No collaborating arrangement is needed. Clonidine hydrochloride (Catapressan(R) tablets - Boehringer Ingelheim Ltd) will be provided by the principal investigator.

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Circ. Res. 1976; 38 : 338-346.

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Inhibition of adrenergic neurotransmission by clonidine: an action on prejunctional α receptors.

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Effect of cholera toxin on pacemaker rate and cyclic adenosine 3' 5' monophosphate in isolated rabbit sinoatrial node.

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SECTION III - BUDGET

vestigators:	% of effort	US $
D. Patte	5%	-
G.H. Rabbani	5%	325.00
ysician hospital	5%	225.00
		Sub total = 550.00

tients hospitalization:

pts x 3 days x 150 Tk. = 18000 Tk. $ 750.00

o. tests:

ool electrolytes

120 x 40 Tk. = 4800 Tk. $ 200.00

ool culture for V. cholerae

40 x 11 = 440 Tk. $ 20.00

pplies - Computer: $ 300.00

Total = US $ 1520.00

Staff commitment : US $ 550.00

Operation: US $ 970.00

ABSTRACT SUMMARY

Clinical study to evaluate the antisecretory effect of clonidine hydrochloride in cholera.

1. This limited study will be conducted in 40 adult patients with severe cholera. The antisecretory effects of clonidine will be examined in one group of 20 patients. 20 other patients without treatment will constitute a control group. The study relies on some experimental evidences showing that the stimulation of α_2 adrenergic receptors may inhibit the effects of cholera toxin in the intestinal mucosa. If positive, this experiment could set the basis of a new pathophysiological approach to cholera.

2. Risks of low blood pressure due to clonidine are moderate in non-hypertensive patients as demonstrated in volunteers. Drop in blood pressure is slight without physical consequences in reclining subject. since reflex control of blood pressure is spared, orthostatic hypotension remains unlikely. Dry mouth is the most uncomfortable side effect of the drug but does not hamper the safety of the trial. Hypertensive crisis at drug withdrawal have been observed only in hypertensive patients with long lasting therapy and are highly unlikely in this trial.

3. Risks will be minimised by carefull selection of the patients excluding those with previous cardiovascular disease or hypertension. Further more the drug will not be administered until rehydration is achieved. Patients will be advised to keep reclining during the trial and to sit for a while before standing, to avoid orthostatic hypotension.

4. Data collection sheets will be kept in a locked place and will only display a serial number. If published, data will show no reference to the identify of the patient.

5. Informed consent (signed or thumb printed) will be obtained from the patients themselves at the time of admission into the study.

6. Does not apply.

7. The direct benefit to the patient will be the cost free treatment of diarrhoeal illness and other disease that may be disclosed during his stay in the hospital.

The society, in general, may take benefit from the identification of a new potential of an already existing drug.

8. This study do not requires the use of records, but will use stool specimens for analysis.

CONSENT FORM

You have been attacked with cholera which provokes a very important loss of water from your body and requires rapid replacement of the lost water. We are testing a drug (clonidine) to cut down the water loss and we propose to you to join the study. If you accept, you will be admitted to our study ward for 3 days. You will be then allocated either to a test group (receiving the drug) or to the control group (not receiving the drug). The amount of passed stools will be regularly recorded and part of it will be taken for analysis. Beside this you will receive adequate treatment according to your condition as any other patient. In addition, if we disclose other disease or parasite, it will be treated free of cost. The drug under trial is a very well known drug which has been safely used for years in other diseases. It may make you feel thirsty and may also induce some dizziness if you stand up quickly from your bed. We therefore recommend you to stay in your bed during the study or to stand up slowly after sitting for 1 or 2 minutes.

If you do not want to be included in the study, you will not be penalised in any way and you will receive proper treatment in the hospital. You also may decide to withdraw from the study at any time.

If you accept to join the study, please sign the consent form here below.

Informed consent:

"After listening the above informations and all my questions having been answered, I accept to be included in this study. I understand that if I decide to withdraw from it, I shall not be refused adequate treatment nor be penalised in any way".

Signature or thumb print

Date: - - - - - - - - - -

সম্মতি পত্র

আপনি কলেরা রোগে আক্রান্ত হয়েছেন। এই রোগে শরীর থেকে অতি প্রয়োজনীয় পানি বের হয়ে যায়। পানি কমে অতি দ্রুত পূরণ করা প্রয়োজন। পানি করণ বন্ধ করার জন্য আমরা একটি ঔষধ (ট্রোনিডিন) পরীক্ষা করছি। আমরা আপনাকে এই পরীক্ষায় অংশগ্রহনের জন্য প্রস্তাব করছি। যদি আপনি সম্মত হন তবে আপনাকে তিন দিনের জন্য হাসপাতালে ভর্তি করা হবে। অতঃপর আপনাকে পরীক্ষার দল (ঔষধ পাবেন) অথবা নিয়ন্ত্রিত দল (ঔষধ পাবেন না) ভুক্ত করা হবে। নির্গত মলের পরিমান নিয়মিত লিপিবদ্ধ করা হবে এবং ইহার অংশ বিশেষ বিশ্লেষণের জন্য নেওয়া হবে। ইহা ছাড়া আপনি আপনার অবস্থা অনুযায়ী যথাযথ চিকিৎসা পাবেন। উপরন্তু আপনার শরীরে অন্য কোন অসুখ বা রোগ-জীবাণু ধরা পড়লে বিনা খরচে ইহার চিকিৎসা করা হবে।

এই গবেষণায় ব্যবহৃত ঔষধ (ট্রোনিডিন) সুপরিচিত এবং ইহা বহু বৎসর যাবত অন্যান্য রোগের চিকিৎসার জন্য নিরাপদ ঔষধ হিসাবে ব্যবহৃত হয়ে আসছে। ইহা ব্যবহারে আপনি পিপাসা অনুভব করতে পারেন এবং বিছানা থেকে হঠাৎ উঠে দাঁড়ালে আপনার মাথা ঘুরতে পারে। তাই আমরা বলবো, এই পরীক্ষায় অংশগ্রহণের সময় আপনি বিছানায় শুয়ে থাকবেন অথবা বিছানায় উঠে ২/১ মিনিট বসার পর আস্তে আস্তে দাঁড়াবেন।

যদি আপনি এই পরীক্ষায় যোগদান করিতে চান, তবে দয়া করে নিম্নের সম্মতি পত্রে স্বাক্ষর দিন।

জ্ঞাত সম্মতিঃ

উপরোক্ত তথ্যাবলী শুনিয়া এবং আমার সকল প্রশ্নের উত্তর দেওয়ার পর আমি স্বেচ্ছায় এই গবেষণায় অনুর্ভুক্তির জন্য সম্মতি দিচ্ছি। আমি অবগত আছি যে যদি আমি আমার নাম এই গবেষণা হইতে প্রত্যাহার করতে ইচ্ছা করি, তবুও আমাকে যথাযথ চিকিৎসা প্রত্যাখান করা হবে না বা আমাকে অন্য কোন ভাবে দন্ডিত করা হবে না।

স্বাক্ষর বা বৃদ্ধাংগুলির ছাপ

তারিখ----------