Attachment 1. Date 20.6.80

REVIEW BOARD ON THE USE OF HUMAN SUBJECTS, ICDDR,B.

Principal Investigator Dr. Asma Khanam Trainee Investigator (if any) _____

Application No. 80-027 Supporting Agency (if Non-ICDDR,B) _____

Title of Study Aspirin as an Anti-Secretory Agent : A Clinical Trial in Cholera.

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
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 Board:
   ___ Umbrella proposal - Initially submit a overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects or 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 Board for review.

We agree to obtain approval of the Review Board on the Use of Human Subjects for any change involving the rights and welfare of subjects before making such change.

Asma Khanam
Principal Investigator

Trainee

80-024
Received.
10.7.80.

SECTION I - RESEARCH PROTOCOL

(1) TITLE: Aspirin As An Antisecretory Agent: A Clinical Trial in Cholera

(2) PRINCIPAL INVESTIGATOR: Dr. Asma Khanam

CO-INVESTIGATOR: Dr. M. R. Islam
Dr. P. K. Bardhan

(3) STARTING DATE: September 1980

(4) COMPLETING DATE: December 1980

(5) TOTAL DIRECT COST: $ 3,708

(6) SCIENTIFIC PROGRAM HEAD:

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

Signature of Scientific Program Head: [signature], Group Secretary, DTHG

Date: 20/6/80

(7) ABSTRACT SUMMARY: The discovery of oral replacement therapy in Cholera has greatly simplified treatment, making effective therapy feasible in all situations. However, in severely affected patients purging occurs at such high rates that intravenous replacement of fluids and electrolytes becomes essential. Aspirin, a potent prostaglandin inhibitor which is extensively used in the general medical practice as an antipyretic and analgesic agent, has been shown to significantly reduce fluid accumulation in the gut of rats and cats exposed to Cholera toxin. Prostaglandin serve as an intermediary for the effects of Cholera toxin in activating intestinal mucosal adenyl cyclase.

This study aims to observe the therapeutic effects of aspirin as an antisecretory agent in human Cholera in a randomized, double blind clinical trial. Thirty adult male of age 15-40 years Cholera

patients who are actively purging at the rate of more than 4 ml/kg/hr would be admitted in the study ward of the Dacca ICDDR,B Clinical Research Centre. A careful baseline measurement of purging will be made followed by administration of aspirin or vitamin c which would be used as a placebo. In cats, the effective dose of aspirin was 25 mg/kg body weight injected into the femoral vein. In this study, aspirin will be administered in the dose of 25 mg/kg body weight orally, not exceeding one gram, the dose being consistent with the dosage used in Rheumatoid arthritis.

(3) REVIEWS:

a) Research involving human subjects: _____

b) Research Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objectives:

To determine whether aspirin has any effect in reducing the purging rate in Cholera.

2. Background:

Despite the successful application of intravenous and oral rehydration in Cholera[1] and the effective shortening of diarrhoea by antibiotic[2] there are many patients who lose fluids so rapidly that without a high rate of intravenous therapy they go into shock and die. So, if a pharmacological agent could be found which safely reduces intestinal fluid secretion, the treatment of cholera could be further simplified and made effective, particularly in the field where intravenous fluids and necessary facilities may not be readily available.

A drug which could be given orally to reduce the massive loss of fluid and electrolytes by antagonizing the effect of cholera enterotoxin on the secretory mechanisms of the small intestine would be of considerable value. Such an agent would simplify the management of cholera, especially in areas with few trained people and equipment[3].

Oral replacement therapy with sugar electrolyte solutions, while being almost 100 percent effective in cases with mild or moderate dehydration, often fails in patients with very intense secretion (4,5,6). An agent that could reduce secretion could help in the success of oral treatment of cholera by oral fluid without the need of intravenous fluid infusion[7].

The vibrio cholerae and escherichia coli organisms cause diarrhoea by the elaboration of enterotoxins which stimulate the small intestinal adenylate cyclase activity. Adenylate cyclase in its turn activates cyclic 3,5 adenosine monophosphate (cyclic AMP) which reduces active absorption of sodium (Na^+) and chloride (Cl^-) through its action on the villous cells at the luminal border and also promotes active secretion of chloride and sodium by the cells of small intestine[8]. It has been

suggested that the effects of the enterotoxin on intestinal cyclic AMP metabolism may be indirect, and that locally synthesized prostaglandin may serve as an intermediary for the effects of the enterotoxin in activating intestinal mucosal adenyl cyclase[9]. It is also conceivable that prostaglandins may be the elusive humoral factor causing diarrhoea in the cholera syndrome by virtue of direct action or by affecting cyclic AMP[10].

Aspirin as an inhibitory agent of prostaglandin synthesis

Some years ago, aspirin was characterized as an "anti-defensive" drug, inhibiting bodily reactions (such as fever, pain and inflammation) that are thought to serve a defensive function. At the same time, it was argued that aspirin acted by inhibiting an unidentified local humoral mechanism that mediated such reactions, and the prostaglandins were named among the humoral mediators possibly involved[11]. In 1971, aspirin and aspirin like drug were shown to inhibit prostaglandin biosynthesis in different preparation from three different species, one being man[12]. Prostaglandin infused into the superior mesenteric artery in dogs causes loss of fluid into the intestine. Prostaglandin E., given orally to man causes diarrhoeas, which was described as normally formed faeces in clear fluid which suggests an effect on intestinal secretion[13].

Vane and his colleagues have shown that acidic anti-inflammatory drugs such as indomethacin or aspirin inhibit the synthesis of prostaglandin in vitro and they suggest that some therapeutic effects are due to this inhibition[12].

Jacoby and Marshall reported that indomethacin, aspirin, and several other anti-inflammatory agents inhibited the cholera toxin induced accumulated of fluid in ileal-ligated rats[14]. Finck and Katz performed a study on cats suggesting that aspirin might prevent the diarrhoea associated with cholera. Three sets of experiments were carried out in isolated small intestinal loops of cats. Cholera toxin was used in first series, both cholera toxin and aspirin in second series, and nothing was used in the third series which was used as control. Effluent was collected from each loop every 30 minutes for 6 hours and then results were compared. There was no statistically signi-

ficant differences in fluid output between the control and cholera toxin plus aspirin group (P 0.01). (15)

3. Rationale:

The drug is easily available, acceptable, cheap and is widely used in medical practice to relieve pain and to alleviate the symptoms associated with certain types of pyrexial illness other than diarrhoea. Aspirin inhibits synthesis or release of prostaglandins, thereby resulting in decreased intestinal fluid loss in experimental animals. If a positive result is obtained in human cholera, it would be of enormous benefits in the prevention of dehydration and resultant suffering and death. It would also be feasible in all situations for the management of cholera by oral rehydration therapy with aspirin requiring fewer numbers of trained people and expensive equipments.

B. SPECIFIC AIMS:

To see whether aspirin can reduce or stop the intestinal fluid secretion in clinical cholera cases.

C. METHODS AND PROCEDURE:

Adult male patients of 15-40 years with acute onset of diarrhoea for 24 hours with moderately severe to swerely dehydration, feeble radial pulse or in shock, and dark field positive will be admitted in the clinical research centre. On admission general clinical examination will be done on all patients to assess the initial dehydration and exclude complication. Patients will be rehydrated with intravenous fluid according to fluid loss, employing a direct measurement of body weight and using a standard intravenous solution only. Adult male patients who do have history of peptic ulcer, asthma or allergy will be disqualified from the study. Standard intravenous therapy, without antibiotics, would be provided throughout the course of hospitalization.

Study patients will be assigned in a double blind, randomized manner to one of the groups: aspirin and vitamin C (as placebo). The tablets will be crushed and dissolved in water so that each ml will contain 25 mgm. After initial rehydration and establishment of baseline purging rates, patients will receive a single dose of one of the two drugs when stool output is in excess of 4 ml/kg/hr

observed within 6 hours after admission. The dose of aspirin will be 25 mg/kg body weight up to a maximum of 1 gm. Same dose of vitamin C will be given 25 mg/kg upto a maximum of 1 gm. This dose is consistent with the dose used in rheumatoid arthritis. If the purging rate increases after an initial decrease, and if it goes up to the level of 4 ml/kg/hr or more, then a similar dose of the same drug will be repeated at 24 hours.

The following observations will be made:

1. Pulse, respiration, B.P., 8 hourly.
2. Intake and output measurement will be taken every 8 hourly until diarrhoea stops.
3. No antibiotics will be given.
4. No restriction of diet or plain water.

Investigations:

1. '0' hr (admission) - F.B. for HCT - Sp.Gr., Stool D/F
   1 drop of blood from finger pulp.
2. Before administration of drug -
   a) Blood for Electrolytes, Sp.Gr., Greatinine, HCT and Platelet count - 3 ml of blood
   b) Stool for occult blood + culture.
3. 2 hours after administration of drug for serum aspirin level determination - 1.5 cc of venous blood
4. Every 24 hours after administration of drug;
   a) Het, Sp.Gr., and platelet count (.25 ml of blood)
   b) Stool for occult blood.

In total 30 adult male, cholera patients with no other complications will be studied. Patients will be considered to have their diarrhoea stopped if no watery stool is passed during the preceeding 24 hours. Patients will be discharged when diarrhoea stops. Treatment for intestinal ova and parasites will be given (if present) at the time of discharge.

Exclusion from the study:

1) Persistent Vomiting
2) Gross electrolyte imbalance
3) Develop any complication, indicating antibiotic intervention
4) Complication after having drug - e.g. allergic manifestation, haematemesis and malaena.

RISKS TO SUBJECTS:

The commonest risk encountered with the use of aspirin is gastric irritation, gastrointestinal bleeding, which will be monitered by history, vital sign record, stool for occult blood test; and careful observation. Occasionally hypersensitivity reaction have been noted.

In order to minimise the hazard of gastric irritation, the drug would be given as a suspension 25 mg/cc taken after food.

DATA ANALYSIS:

We shall analyse the data as follows:

(1) Compare the stool volume over the study period;
(2) amount of I.V. Fluid over the study period;
(3) change of hydration status in between both group by applying statistical significance test.

D. SIGNIFICANCE:

Reduction of fluid losses by an inexpensive, widely used in general medical practice and easily available pharmacologic agent may markedly reduce the need of intravenous fluids in cholera without the help of skilled personnel and equipment and might also help in reducing the oral therapy failures.

E. FACILITIES REQUIRED:

1. 3 beds in the clinical research centre, study ward with nursing coverage.

2. Laboratory space: Existing ICDDR,B laboratory will be utilized.

F. COLLABORATIVE ARRANGEMENTS

Nil

References

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3. Henry I. Jacoby., C.H. Marshall., "Antagonism of Cholera Enterotoxin by Anti - Inflammatory Agents in the rat" NATURE 235: 163 - 165, 1972.

4. Nalin, D.R., Cash, R.A., Islam, R., Molla, M., Phillips, S.R., "Oral Maintenance Therapy for Cholera Patients" J. Pediat. 78: 355-358, 1971.

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8. Field, M., "Acute Diarrhoea in Childhood" (edited by K.M. Elliot and J. Knight) Ciba Fdn. Symp. 1976, pg. 109.

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16. Clinical Pharmacology (Dilling) Stanley Alstead, J. Gordon Macarther. Bailliere, Tindall & Casell, London, 1965, p-307.

SECTION III - BUDGET

A. Detailed Budget

1. Personnel Services:

Name	Position	% of Effort	Project Required Taka	Dollar
Dr. Asma Khanam	Pr. Invest.	50%	7,200	-
Dr. R. Islam	Co-Invest.	5%	2,000	-
Dr. P.K. Bardhan	Co-Invest.	10%	1,440	-
Mr. Mujibur Rahman	Sr. Res. Asstt. Biochem	5%	750	-
Biochemistry Technician		10%	1,000	-
Microbiology Technician		10%	1,000	-
Clinical path. Tech.		10%	750	-
D/F Tech.		10%	750	-
			14,890	

2. Supplies and Materials

Item	Unit Cost	Taka	Dollar
Office Supplies	-	1000.00	-
Printing/Publication	-	3000.00	300
Aspirin Tab. Vit. C Tab.		250.00	-
		4250.00	

3. Equipment : Nil

4. Patient Hospitalization: 30x4xTk. 150.00 = 18,000

5. OPD Care: Nil

6. ICDDR,B Transport : Nil

7. Travel and Transportations of Persons: Nil

8. Transportation of Things : Nil

9. Rent, Communication, and Utilities: Nil

10. Printing and Reproduction: Nil

11. Other Contractual Services: Nil

12. Construction, Renovation, Alterations: Nil

Laboratory Tests	No. of Tests	Cost/Test	Taka	$
1. Blood Electrolytes	30	3.00	90.00	-
2. Serum Creatinine	30	1.20	36.00	-
3. Aspirin Assay	30	5.00	150.00	-
4. HCT, Sp. Gr.	120	2.60 + 6.70	1,236.00	-
5. Platelet Count	90	1.20	108.00	-
6. Stool for Occult Blood	90	1.00	90.00	-
7. Stool for C/S	30	15.50	465.00	-
8. Dark Field for Cholera (Stool)	30	1.00	30.00	-
9. Stool M/E	30	2.05	61.50	-
			1,152.50	

Total -	Tk. 38,292.50	$ 300
30% over head -	11,487.75	$ 90
Grand Total -	49,780.25	$ 390
	($ 3,708)	

B. Budget Summary

Category	Taka	Dollar
1. Personnel	14,890	-
2. Supplies	1,250	-
3. Equipment	-	-
4. Hospitalization	18,000	-
5. Outpatient care	-	-
6. I.C.D.D.R.,B transport	-	-
7. Travel	-	-
8. Transport, things	-	-
9. Rent/communication	-	-
10. Printing/Publication	3,000	300
11. Contractual service	-	-
12. Construction	-	-
13. Lab. Test	1152.50	-
Sub Total	38,292.50	300
30% overhead	11487.75	90
	49780.25	390

$ 3,708

ABSTRACT SUMMARY

This study is designed to determine the efficacy of aspirin as an antisecretory agent in reducing the stool volume in cholera. This will be done as a double blind randomized clinical trial on 30 male adult of 15 to 20 years old cholera patient visiting ICDDR,B, Hospital with moderately to severely dehydration. The patient will be rehydrated by standard intravenous solution (acetate) within 2 hours. If the purging occurs at the rate of 4 ml/kg/hr within 6 hours of admission, a single dose of aspirin and placebo (25 mg/kg body weight not exceeding 1 gm) will be given orally. Aspirin acts by inhibiting the synthesis or released of prostaglandin which increase the fluid secretion in the presence of cholera toxin. If it is found to be effective in reducing the stool volume it will also minimize and simplify the medical care.

1. 30 male adult patients of 15-40 years old with cholera will be selected for the study.

2. There are no psychological, social, and legal risk to this study. Blood will be collected as follows via fingerstick or antecubetal vein:-

   a) After admission 1 drop of blood from finger pulp will be taken for HCT and sp.gr. to assess the dehydration status.

   b) After rehydration and prior to administration of drug, 3 ml. of venous blood will be drawn for electrolyte, sp.gr. creatinine and platelet count.

   c) After administration of drug - .25 ml. of blood from finger pulp will be obtained for HCT, platelet count to assess the risk of gastrointestinal bleeding and repeated every 24 hours until stool is formed.

3. As all patients will be under extensive care we will have sufficient scope to deal with any complications if arises after using aspirin. To minimize the risk we will administer the drug just after food.

4. Confidentiality of the data collected will be ensured. Patient names will not be used in analysis or publication of the data. The original data will be locked in a file in the custody of the principal investigator who will restrict its use.

5. A Bengali written consent form will be taken prior to admission after explaining the methodology and aims of the study.

   a) Not applicable.

   b) Not applicable.

   c) There is very little chance of potential hazard to the patient but even then patient will be kept informed. Necessary treatment will be given if any such complications arises.

6. There is no involvement of interview except to obtain history of onset of illness prior to admission.

7. If aspirin is found to be effective in reducing the stool volume and duration of diarrhoea the cost of medical care will be minimized and simplified also.

8. Hospital records will be used. Small amount of blood will be taken for clinical and biochemical assay as mentioned in clause 2.

CONSENT FORM

ICDDR,B is actively working in the field of diarrhoeal disease to improve and simplify the treatment of cholera and non-cholera diarrhoea. In cholera purging occurs at such high rates that intravenous fluid is needed. The present study aims to utilize the fluid inhibitory effect of a drug "aspirin" in a single dose to a maximum of 1 gram. This drug is quite free from any injurious side effects when ingested in a dose of 25 mg/kg except in very rare occasions, people having ulcer disease may get epigastric pain and gastrointestinal bleeding. Such cases will not be considered for study and provisions will be made for the prompt and proper treatment if it happens in the study cases.

In this study you will have to co-operate with the following tests:-

1. 1 drop of blood will be taken by finger prick just after admission to assess the dehydration status.

2. .25 ml of blood will be taken from the finger tip 24 hours to monitor HCT, platelet count and sp.gr. until stool is formed.

3. After hydration, prior to the administration of the drug 3 ml of venous blood will be drawn to assess the electrolyte, sp.gr. creatinine and platelet count.

4. After 2 hours of administration of drug, 1.5 ml of blood will be drawn from your vein to see how much of the medicine is absorbed in the blood.

5. Stool for occult blood test will be done to determine possible gastrointestinal haemorrhage.

If you like to participate in this study then please sign below. If you do not, usual treatment will not be hampered. You may withdraw your consent at any time which will not disturb routine treatment.

Signature of Investigator

Signature of Patient
or
Thumb print of patient

সম্মতি পত্র

কলেরা এবং উদরাময় রোগের সহজতর এবং উন্নততর চিকিৎসা উদ্ভাবনের জন্য বাংলাদেশ আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র অত্যন্ত সক্রিয়ভাবে কাজ করে যাচ্ছে। কলেরায় তরল পায়খানার পরিমান এত বেশী হয় যে রোগীর শিরা দিয়ে স্যালাইন দেয়া প্রয়োজন হয়ে পড়ে। বর্তমান গবেষণার লক্ষ্য হচ্ছে 'অ্যাসপিরিন' নামক এক ঔষধ ব্যবহার করে কলেরা রোগীদের পায়খানার পরিমান কমানো। এই ঔষধ এক মাত্রায় দেওয়া হবে এবং কোন ক্ষেত্রেই এক গ্রামের বেশী হবে না। শরীরের ওজনের প্রতি কিলোগ্রাম ২৫ মিঃগ্রাম পর্যন্ত ব্যবহারে এই ঔষধে কোন ক্ষতিকারক প্রতিক্রিয়া হয় না। তবে আলসার থাকলে কোন কোন ক্ষেত্রে পেটে ব্যাথা এবং পাকস্থলী ও অন্ত্র থেকে রক্ত করণ হতে পারে। এ ধরণের রোগীদের গবেষণায় নেয়া হবে না এবং এমন কিছু হ'লে তাদের জরুরী এবং ফলপ্রসু চিকিৎসার ব্যবস্থা প্রস্তুত থাকবে।

এই গবেষণায় আপনাকে নিম্নলিখিত পরীক্ষাগুলোর ব্যাপারে আমাদের সংগে সহযোগিতা করতে হবে।

১। ভর্তির পর পরই আপনার শরীরে জলীয় পদার্থ কতটা কমে গেছে এর পরিমাপের জন্য আপনার আংগুল থেকে এক ফোটা রক্ত নেয়া হবে।

২। পায়খানা বন্ধ না হওয়া পর্যন্ত প্রতি ২৪ ঘন্টা অন্তর একবার আপনার রক্তে হিমো-গ্লোবিন, প্যাটিলেট নামক এ ধরণের কোষ ও রক্তের ঘনত্বের পরিমাপের জন্য মাত্র ০.২৫ মিঃলিঃ করে রক্ত নেয়া হবে।

৩। প্রয়োজনীয় পরিমান স্যালাইন দেবার পর এবং আসপিরিন খাওয়ানোর আগে আপনার রক্তে ইলেকট্রোলাইট, রক্তের ঘনত্ব, ক্রিয়াটিনিন ও প্যাটিলেট কোষের পরিমাপের জন্য শিরা থেকে ৩ সিঃ সিঃ মত রক্ত নেওয়া হবে।

৪। ঔষধ খাওয়ানোর দু'ঘন্টা পরে রক্তে কতটা ঔষধ পৌঁচেছে সেটা দেখবার জন্য আপনার শিরা থেকে ১½ সিঃ সিঃ রক্ত নেওয়া হবে।

৫। আমরা আপনার পায়খানাও পরিক্ষা করবো। অন্ত্রে রক্তক্ষরণ হয়ে থাকলে এই পরিক্ষায় ধরা পড়বে।

আপনি এই গবেষণায় অংশগ্রহন করতে চাইলে দয়া করে নিচে সই করুণ। আর না চাইলে স্বাভাবিক চিকিৎসার কোন ত্রুটি হবে না। গবেষণা চলাকালীনও যে কোন সময়ে আপনি গবেষণা থেকে নিজেকে প্রত্যাহার করে নিতে পারেন।

চিকিৎসকের স্বাক্ষর

রোগীর স্বাক্ষর / বৃদ্ধাংগুলের ছাপ

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TABLE I

Comparison of Stool Volumes of Patients after receiving Aspirin & Placebo

roup	No. of Pts.	STOOL VOLUME in ml. (Mean ± S.D.)					
		1st 8 hrs. (8 hrs.)	2nd 8 hrs. (16 hrs.)	3rd 8 hrs. (24 hrs.)	4th 8 hrs. (32 hrs.)	5th 8 hrs. (40 hrs.)	6th 8 hrs. (48 hrs.)
spirin	15						
lacebo	15						

TABLE II

Comparison of I.V. Fluid Requirement after receiving Aspirin & Placebo

Group	No. of Pts.	I.V. Fluid Requirement in ml (Mean ± S.D.)					
		1st 8 hrs. (8 hrs.)	2nd 8 hrs. (16 hrs.)	3rd 8 hrs. (24 hrs.)	4th 8 hrs. (32 hrs.)	5th 8 hrs. (40 hrs.)	6th 8 hrs. (48 hrs.)
Aspirin	15						
Placebo	15						