

MEDICAL DEPARTMENT
Norwich Pharmacal Company
Division of Morton-Norwich Products, Inc.
Norwich, New York

FINAL REPORT

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A STUDY OF THE EFFECT OF BISMUTH SUBSALICYLATE IN PREVENTING
BLOOD LOSS IN CHILDREN WITH JUVENILE RHEUMATOID ARTHRITIS TREATED WITH ASPIRIN

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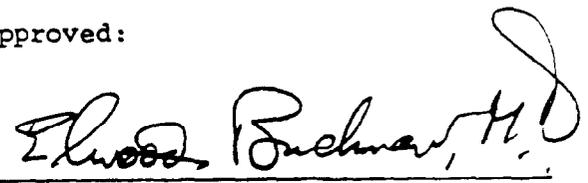
Project No.:
75035-477-73-03-339

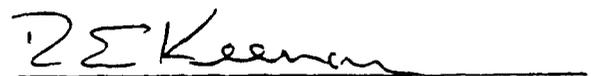
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PURPOSE: To determine whether bismuth subsalicylate, compared to placebo, decreases the gastrointestinal blood loss of children with juvenile rheumatoid arthritis (JRA) on aspirin treatment, using erythrocyte labeling with radioactive Chromium (^{51}Cr). Also, to evaluate the clinical manifestations of gastrointestinal intolerances resulting from aspirin administration, and to evaluate blood salicylate levels.

BACKGROUND:

Aspirin is the drug of choice for the treatment of juvenile rheumatoid arthritis (JRA) (1,2). Other medications such as corticosteroids or non-steroidal anti-inflammatory drugs can be used in special cases but cause more serious toxic effects and greater chronic intolerances than aspirin. Although aspirin is an excellent drug, the extent of the side effects frequently requires stopping its administration. In a recent review of GI side-effects associated with aspirin it was noted that 30% of the JRA patients stopped using the medication.

The most frequent gastrointestinal effects are clinically manifested by abdominal pain and cramps, epigastralgia, nausea and vomiting related to gastric erosion, and occult microbleeding which can provoke hematemesis, melena, anemia and chronic malaise (3,4).

Aspirin disintegrates in the stomach and is absorbed in the proximal small bowel. A number of factors influence the absorption rate which varies with both the patient and the drug. Numerous aspirin formulations are marketed as plain, buffered, or enteric-coated products. Aspirin that is too firmly compressed may disintegrate poorly and may cause increased gastric irritation; even more elegant forms of aspirin may provoke erosion of the mucous membrane.

Some investigators have found less bleeding associated with buffered aspirin, presumably because there are fewer undissolved particles to irritate the GI tract; this has been demonstrated only in healthy subjects and not in patients with painful conditions. The absorption rate of enteric-coated aspirin is quite variable, particularly in children, and may pass through the body without dissolving.

3. Patients were numbered consecutively as they entered the study, and these numbers were maintained for the duration of the study.
4. Patients received bismuth subsalicylate or placebo, as assigned, 10 minutes prior to ingestion of each appropriate dose of aspirin for 4 month study period.
5. The liquid formulations were dispensed in coded, double-blind bottles (coded as A and B: A= bismuth subsalicylate, CN 74237; B= placebo, CN 74238).
6. Patients were assigned, at random, to two study groups, one receiving formulation A first, the other receiving formulation B first.
7. Those patients who received formulation A the first 2 months received formulation B the last 2 months, and vice versa.
8. The dosage levels of bismuth subsalicylate or placebo the patients received were as follows:

3-6 years:	1 teaspoonful 10 minutes prior to aspirin administration
6-12 years:	2 teaspoonsful 10 minutes prior to aspirin administration
Older than 12 years:	3 teaspoonsful (15 ml) 10 minutes prior to aspirin administration
9. Routine clinical reports obtained prior to the study included CBS, urinalysis, sedimentation rate and latex fixation test. Blood salicylate levels were determined prior to study and at bi-weekly intervals during the study(8).
10. In 9 patients, ^{51}Cr tests were done after the 4th week and the 12th week, providing findings for both formulations. Gastrointestinal blood loss was determined with the ^{51}Cr method by Laboratories Clinicos de Mexico (Frontera No. 4) using the technique described by Holt(9). Patients were injected with ^{51}Cr in the morning and 24 hour fecal samples were studied (4 samples/24 hours/subject); samples were collected in appropriate containers, sealed in plastic bags with labels identifying the patient, study number, date and sample number.
11. Side-effects were noted and recorded; if adverse effects persisted, the medication was discontinued.

RESULTS:

Gastrointestinal Bleeding

Nine patients were studied to compare the amount of gastrointestinal bleeding associated with the administration of aspirin with bismuth sub-

Vomiting (Table 3)

Vomiting was reported by 3 (15%) of the patients during the bismuth subsalicylate treatment interval and by 8 (40%) of the patients during the placebo interval. The Wilcoxon matched-pairs signed-ranks test (one-sided) was used and the difference in incidence between the two treatment intervals was significant ($p < 0.01$).

Nausea (Table 4)

Nausea was reported for 10 (50%) of the patients during the bismuth subsalicylate treatment interval and by 9 (45%) of the patients during the placebo interval. The incidence was not significantly different.

Cramps (Table 5)

Cramps was a symptom reported by 2 (10%) of the patients during the bismuth subsalicylate treatment interval and 5 (25%) of the patients during the placebo interval. Comparison of the severity scores of those who suffered cramps by the Wilcoxon signed-rank statistic shows that the severity of cramps was significantly greater ($p < 0.05$) for the placebo group.

Constipation (Table 6)

While none of the patients reported constipation during the placebo treatment interval, 6 (30%) patients reported this symptom during the bismuth subsalicylate interval. Analysis with the two-sided binomial test reveals that the difference in the incidence of constipation is significant ($p < 0.05$).

Overall Upper GI Side-Effects (Table 7)

To permit an evaluation of the overall, upper gastrointestinal disturbances, the findings for all of the symptoms except constipation were pooled. This revealed that 12 (60%) patients experienced some intolerance during the bismuth subsalicylate treatment period while 18 (90%) patients had intolerance during the placebo treatment interval.

Comparison of the total severity scores by the Wilcoxon signed-rank procedure shows that the overall severity of upper gastrointestinal disturbances was significantly greater ($p < 0.005$) during the placebo treatment period than during the bismuth subsalicylate treatment period.

Blood Salicylate Levels

Blood salicylate levels (mg %) were determined at bi-weekly intervals throughout both treatment regimens. Patients were instructed to report to the clinic on the designated day and a blood sample was drawn approximately 2 hours after the early morning dose of medication. The findings for each patient are provided in Tables 8-I and 8-II.

Inspection of the data reveals no clinically significant trends attributable to the two treatment regimens. There were considerable variations in the blood level values of individual patients on both treatments as well as the obvious

Table 1

Blood Loss (ml) According to Treatment as
Determined by ^{51}Cr Technique in 9 Subjects

<u>Patient No.</u>	<u>Aspirin with Bismuth Subsalicylate</u>	<u>Aspirin with Placebo</u>
2	0.8	1.8
4	0.8	1.6
5	2.8	3.6
6	0.3	1.1
8	0.75	1.4
9	1.3	1.3
10	1.0	2.3
11	1.5	2.2
12	0.36	1.3

Wilcoxon T = 0 (p < 0.005)

Table 3

Incidence/Severity of Vomiting According to Treatment¹

<u>Patient No.</u>	<u>Aspirin with Bismuth Subsalicylate</u>	<u>Aspirin with Placebo</u>
1	0	2.5
4	0	0.5
6	0.5	0.5
8	1.0	2.0
12	0	2.0
14	0	2.0
15	0	0.5
17	0	1.0

Wilcoxon T = 0 (p < 0.01)

¹Patients who did not report vomiting are not included in this table.

Table 5

Incidence/Severity of Cramps According to Treatment¹

<u>Patient No.</u>	<u>Aspirin with Bismuth Subsalicylate</u>	<u>Aspirin with Placebo</u>
9	1.5	2.0
12	0	0.5
13	0	0.5
15	1.0	3.0
19	0	1.0

Wilcoxon T = 0 (p < 0.05)

¹Patients who did not report cramps are not included in this table.

Table 7

Incidence/Severity of Any Upper Gastrointestinal Symptoms
(Constipation Omitted) according to Treatment

<u>Patient No.</u>	<u>Aspirin with Bismuth Subsalicylate</u>	<u>Aspirin with Placebo</u>
1	3.0	5.5
2	0	0.5
3	0	0
4	0	1.5
5	4.0	4.5
6	1.0	0.5
7	0.5	1.0
8	3.0	2.5
9	2.0	4.0
10	0.5	1.0
11	0	0
12	0	2.5
13	0	1.5
14	4.5	6.0
15	1.5	4.0
16	0	3.0
17	3.0	4.0
18	0.5	1.0
19	0	1.5
20	1.5	3.0

Wilcoxon T = 8 (p < 0.005)

Table 8-II

Blood Salicylate Levels (mg/%) - Patients Treated with
Aspirin-Placebo Regimen Initially

Patient No.	Aspirin-Placebo Regimen				Aspirin-Bismuth Subsalsicylate Regimen				
	Week 2	Week 4	Week 6	Mean	Week 10	Week 12	Week 14	Week 18	Mean
1	26	22	22	23.3	26	20	20	24	22.5
2	24.8	25.8	27.9	26	28.1	19.9	22	14	21
5	18.6	17.9	16	17.5	18	24	17	-	19.7
10	24	20.4	24.1	23	18	22	15.5	13	17.1
11	12.6	18.3	13.8	15	22	20	20	15.6	19.4
13	4.6	12.3	20	12.3	22	21	22	24	22.3
15	12	16.6	13.2	14	20.9	24	19	27	22.7
16	27	32	28	29	29	24	27	24	26
18	15	23	18	18.7	18	24	21	28	23
20	28	24	27	26.3	32	28	29	26	28.8
Mean:	19.3	21.2	21	21	23.4	22.7	21.3	21.7	22
Range:	4.6-28	12.3-32	13.2-28	12.3-29	18-32	19.9-28	15.5-29	13-28	17.1-28
Median:	19	20	20	19	22	22	20	24	22

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Medical Department
PROTOCOL

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EST. STARTING DATE: March 24, 1975 EST. COMPL. DATE: September 1, 1975

TITLE: "A Study of the Possible Effect of Bismuth Subsalicylate
to Prevent Gastrointestinal Blood Loss in Children with
Juvenile Rheumatoid Arthritis on Aspirin Treatment"

rate is variable and it depends both to drug and patient.

In the market exists a lot of aspirin formulations:

Plain aspirin

Buffered aspirin

Enteric-Coated aspirin, etc.

Aspirin could be as tightly packed that desintegrated badly and it could be a cause for more gastric irritation, but although if is well manufactured provokes the erosion of the mucous membrane - already mentioned. In order to prevent the lesion, buffer aspirin has been tested and some investigators found less bleeding, - presumably because there are fewer undissolved particles that -- irritate the GI tract; nevertheless, this has not been established in patients with painful conditions, but in healthy men. Regarding the enteric-coated aspirin, we will say that, specially in children, the absorption rate is very variable and some even throw - them out without dissolve.

GI side-effects are so common using aspirin that in a recent review 30% of the JRA patients stopped the medication.

Simultaneous administration of antiacids (alumina and magnesium salt or bicarbonate) (5) decrease the blood salicylates levels - due to an elevation of the urinary pH still inside the normal - urine pH ranges.

Some studies performed in animals and in humans (6,7) indicate that bismuth subsalicylate protectively coats the lining of the stomach against gastric irritants (alcohol, cold stress, and aspirin).

of JRA (onset date, type of onset, clinical course, periodic -
evaluation of the articular condition, etc.) aspirine side effects
in patients that already have them or could appear during the treat-
ment.

The patients with known sensitivity to aspirin or to bismuth sub-
salicylate will not participate, neither those that for any com-
plication or illness must receive another drug.

Either those patients that had received with diagnostic purposes
radiactive substances during a year before.

PROCEDURES

1. A crossed double-blind study will be realized in a 4 months -
period.

2. All the patients will receive Bayer Plain Aspirin (containing
0.5 g. of acetilsalicylic acid) accordingly with their weight,
at the mentioned dosis, divided in four dosages, with the --
following schedule:

6:00 a.m.

12:00 p.m.

6:00 p.m.

12:00 a.m.

3. Consecutive numbers will be assigned to the patients, as they
enter in this investigation and they will mantain this number
along the study.

4. The patients will receive bismuth subsalicylate, elaborated

The test ⁵¹ Cr will be also included to study occults loss blood in feces, in 8 of the patients. This laboratory test will be realized a month after the medication starting (bismuth subsalicylate or placebo) and after the third month, when the patient had changed of group, this means, a month after his change.

10. The plasmatic salicylate levels as the ⁵¹ Cr will be realized by Laboratorios Clínicos de México (Frontera No. 4) using for the technique described in the separate appendix.

The patients will be injected with ⁵¹ Cr during the morning of a day and then the 24 hours fecal samples will be studied, obtained a total of 24 hours four samples for patient.

The collection of the fecal sample will be done in bottles of black plastic material (furacin jarks), which will be put in plastic bags to be closed with labels, in which appears the name of the patient, his number, date and number of samples (from 1 to 4).

11. Eventually side-effects will be registered and if serious adverse effect presents, the medication will be stopped.

FINAL REPORT

At the completion of the study a final report will be prepared discussing the design of the study, results, adverse or omitted data and will include each subject's history and physical examinations and laboratory results.

PUBLICATIONS