J. Lab. & Clin. Med.
December, 1969

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Absence of gastrointestinal bleeding following administration of salicylsalicylic acid

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A double-blind investigation in 12 normal subjects was conducted to determine gastrointestinal blood loss associated with ingestion of a placebo, salicylsalicylic acid, acetylsalicylic acid, and a combination of the 2. Blood loss was measured by labeling the normal subject's red blood cells with Cr^{51} and counting the radioactivity in the stool during 8 day randomized collection periods for each drug and placebo. Salicylsalicylic acid did not produce any bleeding above the control value determined during administration of lactose placebo tablets, whereas acetylsalicylic acid produced a blood loss averaging 4.8 ml. per day. The combination tablet of the 2 (which contains only a small amount of acetylsalicylic acid) produced minimal blood loss, 1.2 ml., as compared to 0.6 ml. per day with the placebo. This study demonstrates the sensitivity of the radioactive chromium method for detecting bleeding caused by low doses of acetylsalicylic acid and shows that not all salicylates cause gastrointestinal bleeding.

The drug of first choice when analgesic and anti-inflammatory actions are called for is salicylate, despite the well-known limitations of the usual forms of this drug. Many attempts have been made to modify the salicylate formulation and to develop derivatives so as to increase the amount which can be given at one time without causing unwanted side effects and to prolong the salicylate action beyond the usual duration. Apart from the desirability of maintaining adequate salicylate blood levels, a major concern has been to find a preparation with a maximum of gastric tolerance and particularly one that would cause minimal or no gastrointestinal bleeding.

Numerous studies in man and animals have shown that oral administration of aspirin can cause gastrointestinal blood loss.[1–4] The mechanism by which

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Received for publication Jan. 6, 1969.
Accepted for publication Sept. 12, 1969.

aspirin causes gastrointestinal bleeding has not been firmly established. A direct action on the gastric mucosa seems likely, and this concept is supported by the absence of gastric symptoms when aspirin is given in the form of enteric-coated tablets,[5] which are formulated to resist dissolution in gastric fluids but to dissolve readily in intestinal fluids. Enteric-coated tablets, however, have poorly reproducible absorption characteristics, the transfer of such tablets from stomach to intestine being essentially a random process.[6]

Previous work from this laboratory[3] has shown that a buffered solution of sodium acetylsalicylate does not cause bleeding, probably because there is no contact of un-ionized acetylsalicylic acid with the gastric mucosa.

Another approach to eliminating the harmful effects on the stomach would be a salicylate that is practically insoluble in gastric contents, but soluble in the small intestine. Such a compound is salicylsalicylic acid, whose solubility at pH 1 is less than 0.1 mg. per milliliter but which is freely soluble at neutral pH. Physical-chemical and clinical characteristics of this salicylate have been described.[7-10] They show that salicylsalicylic acid is somewhat more slowly absorbed than sodium salicylate and aspirin, that it is converted to salicylate, in the body, and that its clinical activity is comparable to that of sodium salicylate. It was, therefore, thought advisable to determine the effect of this compound on gastrointestinal bleeding. Since this material is available in a commercial product as a mixture of salicylsalicylic acid and aspirin,* it was thought to be of enough interest to be included in this study. Several clinical studies have substantiated the effectiveness of this preparation.[11-13]

Materials and methods

Twelve healthy volunteers with no history of gastrointestinal complaints and with normal hematocrit levels were selected for this study. Ages ranged from 19 to 33 years. There were 11 men and one woman.

Twenty milliliters of venous blood were drawn from each subject and mixed with a 5 ml. acid citrate dextrose solution (Abott No. 6761) containing 300 μc of Cr^{51} (as sodium chromate, Abott No. 6716). After 30 minutes at 37° C., the mixture was reinjected intravenously into the same subject. This amount of Cr^{51} assures sufficient radioactivity in the blood to enable accurate measurements to be taken up to 8 weeks from labeling. Stool collections were begun 2 days later and continued for 50 days.

Four sets of tablets were prepared and code-marked for this study. Formulation A contained acetylsalicylic acid (aspirin), 840 mg. per tablet. Formulation B was a lactose placebo. Formulation C was the combination tablet, containing salicylsalicylic acid, 486 mg., and acetylsalicylic acid (aspirin), 162 mg. per tablet. Formulation D contained salicylsalicylic acid, 602 mg. per tablet. Tablets A, C, and D contained equivalent amounts of salicylic acid when hydrolyzed. All tablets were uncoated and of identical size, shape, and color.

The study was carried out in a double-blind fashion with the use of a Latin square design. Neither the author and his associates nor the subjects knew which preparation was which. Only after all data had been collected and tabulated was the code broken.

The 4 sets of test tablets were administered in a randomized rotation manner. Subjects were instructed to take one tablet after each meal and one or two tablets at bedtime (one tablet for subjects weighing up to 160 pounds, two tablets for those weighing 160 pounds or over). They were told not to take aspirin or other drugs during the study. Their educational background and experience (medical students, teachers, and technicians) justifies the assump-

*Persistin, Sherman Laboratories, Inc., Detroit, Mich.

Table I. Average total blood loss, milliliters per day*

Subject	*Weight*	*Tablets per day (No.)*	*Tablet A (A.S.A.,† 840 mg.)*	*Tablet B (lactose placebo)*	*Tablet C (S.S.A.,‡ 486 mg.; A.S.A., 162 mg.)*	*Tablet D (S.S.A.,‡ 602 mg.)*
R. K.	175	5	4.0	0.5	0.9	0.6
R. N.	175	5	13.7	1.2	2.0	1.0
A. T.	159	4	3.2	1.5	1.7	1.6
M. J.	184	5	1.9	0.8	1.6	0.6
P. P.	150	4	3.0	0.5	0.6	0.3
J. M.	230	5	1.6	0.4	0.6	0.3
F. M.	205	5	17.4	0.5	2.1	1.0
M. B.	140	4	2.2	0.3	1.0	0.7
B. E.	120	4	1.1	0.1	0.5	0.3
A. O.	185	5	1.2	0.7	0.6	0.4
J. H.	165	5	3.7	0.8	1.3	0.9
R. J.	160	5	N.T.§	0.2	N.T.§	0.2

*Averages (± standard error), 4.8 (±5.2), 0.6 (±0.4), 1.2 (±0.5), and 0.7 (±0.4) for A, B, C, and D, respectively. Comparisons: B vs. A, $P < 0.05$; B vs. C, $P < 0.01$; B vs. D, $P > 0.10$; C vs. D, $P < 0.01$.
†A.S.A. denotes acetylsalicylic acid.
‡S.S.A. denotes salicylsalicylic acid.
§Not tested.

tion that these instructions were followed. Subjects received each of the 4 test preparations for 8 day periods, interspersed with 6 day rest intervals. Stools were collected beginning one day after the start of each 8 day tablet period and ending one day after the last day of this period. Fecal examinations made at the end of each rest interval confirmed normal blood loss values for each subject before the next period of tablet administration.

Each stool specimen was homogenized in a Waring Blendor with twice its weight of water. A 90 Gm. aliquot of the homogenate was counted in a scintillation spectrometer.* One milliliter samples of blood were drawn every 5 days and were counted at the same time as the stool samples. Blood loss from the stool was calculated from the formula:

$$\text{Blood in stool, milliliters} = \frac{\text{counts per minute per gram of stool homogenate}}{\text{counts per minute per milliliter of blood}} \times \text{weight of stool homogenate.}$$

The blood count per minute value used in these calculations was that of the blood sample drawn at the time closest to each stool collection. Blood loss data reported are average values from stools collected during the 8 day periods.

Results and discussion

This study was undertaken to determine gastrointestinal bleeding associated with the ingestion of a placebo, salicylsalicylic acid, aspirin, and a combination tablet containing salicylsalicylic acid and aspirin. The results are presented in

*Manufactured specially by Harshaw Chemical Co., Cleveland, Ohio, to accommodate a 20 by 100 mm. plastic Petri dish between two 5 inch crystals.

Table I and indicate that there was no bleeding above control values after ingestion of salicylsalicylic acid.

Although there is a statistically significant difference (by paired t test) between the blood losses induced by the salicylsalicylic acid—aspirin combination (C) and the placebo (B), the average difference is only 0.6 ml. per day and is indicative of very minimal blood loss caused by this preparation.

Parenthetically, it may be noted that the experimental methods used in this study were sensitive enough to detect the effect of relatively small amounts of acetylsalicylic acid, namely, 648 to 810 mg. per day. The fact that salicylsalicylic acid does not cause gastrointestinal bleeding may be because salicylate-induced bleeding occurs in the stomach rather than the intestine and that the compound is not soluble in gastric secretion but is dissolved in and absorbed from the small intestine. Alternatively, the acetyl group in the acetylsalicylic acid, which is absent in salicylsalicylic acid, may be responsible for gastrointestinal bleeding.

It is of interest that subjects R. N. and F. M. lost more blood while taking acetylsalicylic acid than the others. This is probably due to a greater sensitivity of the stomach mucosa to the drug since careful questioning did not reveal other possible causes such as respiratory infections, excessive consumption of alcohol, bleeding from nose or gums, diarrhea, constipation, or the taking of other drugs. None of the stools contained fresh blood.

Data to be reported later indicate that plasma salicylate levels are of the same order of magnitude after ingestion of salicylsalicylic acid as after aspirin.

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