Fecal Blood Loss and Plasma Salicylate Study of Salicylsalicylic Acid and Aspirin

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Salicylsalicylic acid (salsalate) and acetylsalicylic acid both hydrolyze to yield salicylic acid, considered to be the active moiety of these drugs. Salsalate was originally developed as a safer alternative to aspirin. Subsequent studies by Leonards,[1] Thune,[2] and Edmar[3] indicated that salsalate has no more gastric blood loss liability than placebo. In addition, lower doses of salsalate are sufficient to provide clinically effective blood levels of salicylate[4-6] because upon hydrolysis salsalate yields 28 per cent more salicylate than aspirin when equal weights are used.

These two factors, blood loss and dosage, assume clinical significance in long-term salicylate therapy widely used in the rheumatic diseases. If salsalate does indeed possess these two attributes, patients who take large doses of aspirin for long periods of time might materially benefit from the alternative employment of salsalate. With this in mind, we undertook the following controlled study comparing placebo with salsalate* and aspirin to determine the propensity of both drugs to induce gastric erosion in a group of volunteer subjects. As a corollary, we sought to verify that adequate plasma salicylate levels could be obtained with lower doses of salsalate.

From the Peninsular Testing Corporation, Miami, Fla. Supported by a grant from Riker Laboratories, Inc.

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Methods and Materials

This study had two objectives: one, to assess fecal blood loss (chromium-tagged RBCs) after prolonged treatment with either salsalate or aspirin; two, to determine daily plasma salicylate levels during the study and for 36 hours (at 12-hour intervals) after the last dose.

A placebo-controlled study design was selected. Twenty healthy male volunteers between 21 and 50 years of age were enrolled as subjects. Their health status was assured by history and physical and laboratory examinations. History, among other things, ruled out anorectal disease productive of blood loss (confirmed by proctoscopy), frequent aspirin use or intolerance, excessive alcohol use, or past ulcerative colitis, regional enteritis, or gastrointestinal bleeding. Physical examination included a check of all systems and vital signs and relevant non-invasive procedures such as auscultation, otoscopy, ophthalmoscopy, and visual study of mouth, nose, and dermal areas. Laboratory evaluations consisted of standard urinalysis, hematology, and blood chemistry studies and, in addition, RBCs for ^{51}Cr count, 96-hour stool collection for ^{51}Cr count, and a daily test for fecal occult blood.

Subjects were housed during the entire 23-day course of the study in a clinical research facility. All administration of test drugs and specimen collections were

carefully monitored by attendants. Placebo and drug administration continued for three consecutive weeks, three times a day prior to each meal at 8 A.M., 2 P.M., and 8 P.M. Two salsalate tablets (500 mg each) or four aspirin tablets (325 mg each) were given on a t.i.d. basis. The intentional disparity in doses between the two drugs was designed to provide approximately equivalent amounts of salicylate for absorption because salsalate yields two, not one, molecules of salicylate upon hydrolysis.

Blood Loss Study

Once assured of a subject's healthy hematologic, renal, gastrointestinal, and hepatic status, individuals were reinjected with a suspension of their own RBCs which had been "labeled" with ^{51}Cr as $^{51}CrO_4$. Total dosage of radioactivity was about 300 microcuries. An RBC survival curve was established by appropriate examination of blood specimens throughout the study. Baseline fecal blood loss values were determined during an initial week of placebo administration. Twenty-four-hour fecal specimens were collected during the last four days (i.e., days 4, 5, 6, and 7) of that week and during a similar period for each of two subsequent weeks of treatment with the active drugs (total three weeks). All fecal specimens were subsequently analyzed for ^{51}Cr content. Complete details of the procedures used are described by Powsner,[7] Phillips et al.,[8] and Beeken.[9]

Blood loss determinations were interpreted as normal at less than 1 ml per day, suspicious at 1 to 3 ml per day, and abnormal at more than 3 ml per day.

Plasma Salicylate Levels

Procedures used for these determinations were adapted from Brodie et al.[10] and Routh et al.[11] During the three-week study, all blood specimens were taken shortly before the morning drug dose at 8 A.M., that is, 12 hours after the last dose of the previous day. All salicylate values, therefore, reflect blood levels 12 hours after the preceding dose. The only exceptions to this scheme were two of the last three specimens taken after the final dose of week 3, at 24 and 36 hours. Plasma salicylate concentrations were determined as follows: week 1 (placebo), on day 6; weeks 2 and 3 (drug), on days 3, 4, 5, and 6; week 4 (postdrug), at hours 12, 24, and 36.

The subjects' weight and vital signs were monitored daily, 2 hours after the morning dose. Drug tolerability and incidence of adverse reactions were also monitored on a daily basis. Laboratory tests were repeated at the end of placebo treatment and also at the end of each drug-treatment week. Any laboratory tests found to be abnormal were repeated within 24 to 48 hours.

Statistical methodology employed in analysis of data in this study included analysis of variance, Student's *t*-test, and Newman–Keuls procedures. Throughout, 5 per cent was considered the acceptable level of statistical significance.

Results

During this long trial, no subject was dismissed either for intercurrent illness or failure of compliance with study guidelines. The 20 subjects proved to be a homogeneous population (Table I). For salsalate and aspirin groups, mean ages were 25.9 and 26.6 years, mean weights were 71.6 and 67.8 kg, and mean heights were 177.27 and 172.48 cm, respectively.

Weekly blood loss was determined by the average of four readings taken on the last four days of each week. Analysis of variance indicated a significant difference between the two active drugs and between the weeks for aspirin. Differences during the week 1 placebo treatments were not significant; however, there were significant differences in blood loss levels

TABLE I

Subject Statistics

Parameter	Salsalate group	Aspirin group
Age (yrs)		
Mean	25.90	26.60
S.D.	6.14	6.93
Weight (kg)		
Mean	71.60	67.80
S.D.	7.53	8.04
Height (cm)		
Mean	177.27	172.48
S.D.	9.08	4.99

between salsalate and aspirin during the second and third weeks (Table II). Week 2 values for salsalate were 0.709 ml per day and for aspirin, 9.830 ml per day; respective values for week 3 were 0.659 and 7.723 ml per day. Blood loss after aspirin was greater than after salsalate ($P < 0.01$). Further analysis using the Student's *t*-test indicated that aspirin patients had significantly higher blood loss during the second and third weeks than during the control week ($P < 0.01$). Salsalate values were no higher than those of control.

It is interesting to visualize the pattern of daily fecal blood loss in addition to the weekly mean fecal blood values displayed in Fig. 1. Data points during placebo administration (week 1) reveal consistent values at less than 1 ml per day. In week 2, however, the aspirin effect is clear and prominent, rising to almost 11 ml per day by the fifth day of that week. Although modest decreases occurred during the third week, aspirin blood loss values remained consistently in the abnormal area while those for salsalate differed only minutely from those of placebo.

Following active drug ingestion in week 2, plasma salicylate levels promptly rose to the therapeutic range. Except for the final value, representing levels 36 hours after the final dose of either salsalate or aspirin, all others exceeded placebo to a highly significant degree ($P < 0.01$) (Table III). Highest plasma salicylate was achieved in week 2 on day 5; at that time salsalate values were 15.98 mg/dl and aspirin values were 17.40 mg/dl. In-

TABLE II

Weekly Blood Loss for Salsalate and Aspirin

	Weekly blood loss (ml/day)		*P* Values
	Placebo group		
Week 1			
Mean	0.627	0.557	NS
S.D.	0.534	0.344	
	Salsalate group	Aspirin group	
Week 2			
Mean	0.709	9.830	$P < 0.01$
S.D.	0.382	6.695	
Week 3			
Mean	0.659	7.723	$P < 0.01$
S.D.	0.224	4.486	

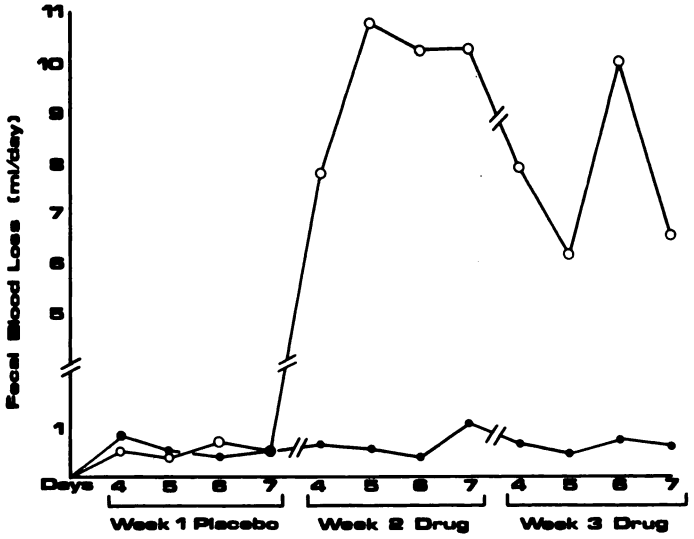

Fig. 1. Salsalate and aspirin group mean fecal blood loss values (ml/day) during one week of placebo and two weeks of active drug ingestion: (●——●) salsalate; (○——○) aspirin.

explicably, although dosage and all other factors remained constant, plasma values for both drugs fell to a low point of 9.43 and 10.22 mg/dl for salsalate and aspirin, respectively, on day 3 of week 3. Salicylate concentrations for both drugs were statistically no different throughout the entire test period. They were also consistently over 10 mg/dl (except day 3 for salsalate: 9.43 mg/dl) despite the fact that blood specimens were always taken 12 hours after the last dose of the day before. In posttreatment week 4 plasma concentrations were 9 mg/dl for both drugs at 12 hours; at 24 hours, salsalate was 4.37 mg/dl and aspirin was 3.43 mg/dl; while at 36 hours, values for both drug levels were not significantly different than those for placebo.

Side effect compilation was complicated by upper respiratory infection occurring in 12 of the 20 subjects. However, analysis of all adverse reports failed to show a preponderance meaningfully associated with either drug; the effects seemed random. Even those possibly drug related (Table IV) failed to cluster in one treatment group or the other. Headache, the most prominent effect reported, occurred in seven subjects. Interpretation, though, was obscured in that four of these seven individuals also had upper respiratory infections during much of this study.

Liver enzyme changes were seen in three subjects, all of whom started the study with mildly elevated SGOT levels. One also had a borderline GGT. Another had an initial decrease in SGOT after two days of aspirin (3900 mg/day), then a modest rise after seven more days. This began to level off 12 hours after the final drug dose. The subject was asymptomatic except for an infected wisdom tooth. Two subjects had SGOT changes and remained in the study. Both were taking salsalate (3000 mg/day). Enzyme changes began during the placebo period in both individuals. Follow-up tests during and after the trial showed slow but steady decreases to normal values. Physical examination was unremarkable except for

TABLE III

Plasma Salicylate Concentrations (in mg/dl)

Drug group	Week 1 (placebo) Day 6	Week 2 (treatment) Day 3	Week 2 (treatment) Day 4	Week 2 (treatment) Day 5	Week 2 (treatment) Day 6	Week 3 (treatment) Day 3	Week 3 (treatment) Day 4	Week 3 (treatment) Day 5	Week 3 (treatment) Day 6	Week 4 (posttreatment)* Day 1	Week 4 (posttreatment)* Day 1	Week 4 (posttreatment)* Day 2
Salsalate												
Mean	0.240	10.490	14.290	15.980	11.290	9.430	10.840	12.170	10.900	9.040	4.370	0.980
S.D.	0.344	3.464	5.549	5.845	4.349	4.337	4.958	5.788	4.786	4.392	3.879	1.008
Aspirin												
Mean	0.150	11.480	14.900	17.400	11.790	10.220	11.240	13.010	11.080	9.260	3.430	0.420
S.D.	0.178	2.561	3.868	4.346	2.879	2.819	2.662	3.442	3.457	2.929	1.649	0.669

* Days 1 and 2 readings were at 12, 24, and 36 hours, respectively, after last drug dose.

the presence of upper respiratory infection.

None of the enzyme changes noted in these three subjects was "markedly abnormal," that is, three times the upper limit of normal. Nor did they meet the other criteria for withdrawal from a study established recently at the Hepatotoxicity Fogarty International Conference.[12]

Discussion

Wide clinical experience with salicylates has given this class of drugs a prominent place in therapy. This is especially true in the rheumatic disorders. However, the problem of gastric erosion and bleeding continues to plague ongoing aspirin therapy. Current reappraisals of the salicylate derivative salsalate provide convincing evidence of an effective and safer alternative.

In part, this evidence results from earlier studies. Leonards,[1] using ^{51}Cr-labeled RBC methodology, found that salsalate did not produce any gastrointestinal blood loss above that of placebo control values. Aspirin caused blood loss of 4.8 ml per day; a combination of 486

TABLE IV

Side Effects

Side effect	Salsalate	Aspirin
Headache	2*	5**
Rash, groin	1	0
Heartburn	0	2
Abdominal cramp	1	0
Nausea	3	1
Blood at stool	0	1†
Emesis	1	1
Upset stomach	0	1

* One associated with upper respiratory infection.

** Three associated with upper respiratory infection.

† Subject reported blood on toilet paper. Test for fecal blood (hemoccult) negative.

mg salsalate and 162 mg aspirin caused intermediate levels of blood loss—1.2 ml per day. Another investigator, using a direct visualization technique (gastrocamera), found a large quantity of pinhead-sized blood clots in the stomachs of all subjects taking aspirin, whereas after salsalate administration only separate small blood clots were observed in one subject.[3] Thune in 1968, using a modified benzidene test, found no evidence of blood loss in a group of 22 rheumatoid and osteoarthritis patients taking salsalate.[2]

Our own study of blood loss after taking salsalate or aspirin corroborates these investigations and provides a sound basis for clinical use of the former in prolonged therapy. In addition, our findings on the plasma salicylate levels attained with these two drugs indicate that about 30 per cent less salsalate need be used to reach effective drug concentrations. Two recent studies have confirmed this.[6]

Taken in the light of our own and previous work, then, available data indicate that salsalate is safer than aspirin in terms of gastric irritation and that smaller amounts of drug are necessary to achieve adequate and therapeutically effective blood levels of salicylate. Such findings should be studied with care by clinicians seeking safer modes of treatment for their arthritic patients.

Summary

Using a placebo-controlled methodology, 20 healthy volunteers housed in a clinical research facility for 23 days were studied for fecal blood loss and plasma salicylate levels after taking salsalate (salicylsalicylic acid) or aspirin. Daily dosages were 3000 mg salsalate or 3900 mg aspirin. Aspirin produced statistically significant gastrointestinal blood loss over control levels and over that produced by salsalate ($P < 0.01$). Blood loss with salsalate was not different than that with placebo. Despite the intentional disparity of dosages between the two drugs, plasma salicylate levels were not statistically different. Side effects occurred at about equal frequency with either drug. Most prominent were headache and nausea. However, concomitant upper respiratory infection in 12 subjects rendered interpretation difficult.

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