Biopharmaceutical Aspects of Aspirin-Induced Gastrointestinal Blood Loss in Man

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Abstract □ The extent of injury of the gastrointestinal mucosa due to contact with aspirin (ASA) particles is likely to be a function of contact area and duration of contact, among other factors. While the *duration* of contact between ASA particles and mucosa may be shortened by decreasing the particle size of the drug and thereby increasing its rate of dissolution, this results in an increased *area* of contact between the drug and the mucosa. It is impossible to decrease both duration and area of contact by particle size adjustment. One method by which contact time can be shortened, without simultaneously increasing the area of contact, is the addition of antacids ("buffers") to ASA tablet formulations. Other formulation variables being the same, these additives should increase the rate of ASA dissolution and thereby decrease the time of contact between the drug particles and the gastrointestinal mucosa. Average daily occult blood loss in the stool was determined in healthy human subjects who received different ASA tablet preparations. Two of these preparations were very similar in their *in vivo* absorption characteristics, but differed in that one contained relatively small particles of ASA and no antacids, while the other type contained larger ASA particles and antacids. The ASA-antacid tablets produced significantly less bleeding than the ASA tablets which did not contain the additives.

Keyphrases □ Aspirin-induced gastrointestinal bleeding—biopharmaceutic aspects □ Antacid effect—absorption rate, aspirin-induced bleeding □ Particle size effect—absorption rate, aspirin-induced bleeding

There is now considerable evidence that aspirin-induced gastric or gastrointestinal occult bleeding is usually a local effect resulting from contact of aspirin particles, or of the saturated solution of aspirin surrounding these particles, with the mucosa (1–4). The most direct support for this conclusion derives from the recent observation that repeated intravenous administration of aspirin to healthy human subjects caused no bleeding while similar doses given orally in tablets produced appreciable occult blood loss (3). This being the case, it was a reasonable assumption that the extent of mucosal injury and bleeding due to aspirin might be modified by pharmaceutical dosage form factors. A series of studies was initiated therefore to determine the effect of dosage form on occult gastrointestinal blood loss due to aspirin in man. One of these studies dealt with the effect of buffer capacity on the blood loss produced by aspirin solution (4) and another was concerned with the effect of particle size on the gastrointestinal bleeding resulting from aspirin tablets (2). The latter study yielded results consistent with the assumption that the degree of mucosal injury from aspirin is a function of both the area and duration of contact of the drug particles with the mucosa (2).

The duration of contact may be shortened by decreasing the particle size of aspirin and thereby increasing its rate of dissolution. However, this also causes an increase in the area of contact which apparently offsets the advantage gained by decreasing the contact time (2). One way to circumvent this reciprocal relationship is to increase the dissolution rate of aspirin by the addition of antacids to the tablet formulation. Even relatively small amounts of such additives, though insufficient to modify appreciably the pH of the gastric fluids, will raise the pH in the immediate "microenvironment" of the aspirin particles and thereby increase their rate of dissolution (5). All other factors being the same, it should therefore be possible to reduce aspirin-induced

Table I—Physicochemical Properties of Aspirin Tablets Used in the Study of Gastrointestinal Bleeding

Type of Tablets	pH of Dispersion[a]	Amount in Soln., mg./30 ml.[a]	"Paste pH"[b]
Aspirin, tablets (*E*)[d]	2.7	128 (130)[c]	1.1
Aspirin + antacid Commercial tablets (*F-I*)[e]	5.2	915 (938)	5.2
Aspirin + antacid Experimental tablets (*F-II*)[f]	6.9	898 (953)	5.4

[a] Three tablets, each containing 0.32 g. aspirin, were dispersed in 30 ml. distilled water and the dispersion was agitated for 3 hr. at 27 ± 1°. Data are averages of four experiments. [b] The pH of a paste made of crushed tablets and 0.1 *N* HCl (5). [c] The amount stated in parentheses includes free salicylic acid (in terms of aspirin), most of which was formed during the 3-hr. agitation. [d] These tablets are referred to in Tables IV and V as *E-I* and *E-II* merely to distinguish two groups of experiments. [e] Aspirin 0.32 g., aluminum glycinate 0.05 g., magnesium carbonate 0.1 g./tablet. [f] Aspirin 0.32 g., magnesium carbonate 0.32 g./tablet.

Table II—Gastrointestinal Bleeding Produced by Rapidly Absorbed Commercial Aspirin-Antacid Tablets (*F-I*) and by More Slowly Absorbed Regular Aspirin Tablets (*E*)

Subject	Age, yr.	Sex	Body Weight, kg.	Average Daily Blood Loss, ml. Control	Aspirin–Antacid	Aspirin
7	29	M	98	0.7	1.6	4.3
8	26	M	81	0.5	4.3	3.4
9	32	M	77	1.1	1.3	1.7
10	29	M	75	0.7	1.7	1.6
11	29	M	100	0.5	0.9	1.5
12	49	M	62	0.6	1.9	2.8
Average	32		82	0.7	2.0	2.6

Table III—Gastrointestinal Bleeding Produced by Rapidly Absorbed Experimental Aspirin-Antacid Tablets (*F-II*) and by More Slowly Absorbed Regular Aspirin Tablets (*E*)

Subject	Age, yr.	Sex	Body Weight, kg.	Average Daily Blood Loss, ml. Control	Aspirin–Antacid	Aspirin
1	24	M	68	0.5	2.7	3.5
2	25	F	49	0.3	1.2	4.3
3	24	F	77	0.4	2.7	4.5
4	18	F	61	0.4	1.2	1.7
5	27	F	59	0.5	4.7	11.4
6	21	M	68	0.3	4.1	1.9
Average	23		64	0.4	2.8	4.6

Table IV—Summary of Three Studies on the Effect of Dosage Form on Aspirin-Induced Gastrointestinal Bleeding in Man

Dosage Form	Code Designation	Absorption Characteristics: $t_{50\%}$, min.[a]	Absorption Characteristics: No. of Subjects	Gastrointestinal Bleeding: Total Daily Blood Loss, ml.	Gastrointestinal Bleeding: Total Minus Control, ml.	No. of Subjects
Control	*A*	—	6[b]	0.5		12[b]
Placebo tablets		—		0.6	0.1	
Aspirin, large particles (experimental tablets)	*B*	52		3.4	2.9	
Aspirin, fine particles (experimental tablets)	*C*	11		4.7	4.2	
Control	*D-I*	—	12[c]	0.7		6
Aspirin, small particles (commercial tablets)	*E-I*	23		2.6	1.9	
Aspirin, small particles and antacid (commercial tablets)	*F-I*	12		2.0	1.3	
Control	*D-II*	—	6	0.4 (0.4)		5 (6)[d]
Aspirin, small particles (commercial tablets)	*E-II*	17.5		3.2 (4.6)	2.8 (4.2)	
Aspirin, small particles and antacid (experimental tablets)	*F-II*	9.5		2.4 (2.8)	2.0 (2.4)	

[a] Time for 50% absorption minus apparent lag time. [b] From Leonards and Levy (2). [c] From Levy, Leonards, and Procknal (7). [d] Bleeding data in parentheses represent average of six subjects; the data outside the parentheses exclude one unusually heavy bleeder (Subject 5 in Table III).

occult bleeding by the addition of antacids to aspirin tablets. A test of this proposition is complicated by the fact that formulation variables other than the presence or absence of antacids can also modify appreciably the *in vivo* dissolution characteristics of aspirin tablets. In the study to be described here it has been possible to compare the amount of gastrointestinal blood loss produced by two types of aspirin tablets which were absorbed at similar rates. One type contained relatively small (smaller than 80 mesh) particles of aspirin and no antacid while the other contained larger particles of drug as well as antacid. The similarity in their *in vivo* absorption characteristics may be attributed to the fact that the rapid dissolution of aspirin in one tablet preparation was due to a larger specific surface area of the drug, while in the other tablet preparation it was the result of the higher microenvironmental pH due to the antacid. A comparison of the occult blood loss produced by these two preparations permits a direct assessment of the possibility of reducing aspirin-induced gastrointestinal bleeding by the addition of antacids to aspirin tablets.

EXPERIMENTAL

The test panels consisted of healthy men and women with no history of gastrointestinal disease and with normal hematocrit levels. Their red blood cells were labeled with Cr^{51} as described previously (2) and all stools were collected throughout the study. Gastrointestinal blood loss was determined from the radioactivity of the stool in relation to that of the blood (2). The absorption of aspirin from the various tablet preparations was calculated by the Wagner-Nelson method based on the concentrations of total salicylate in the plasma as a function of time (2, 6). The "absorption $t_{50\%}$" is defined as the time for 50% absorption minus the apparent lag time. The experimental aspirin tablets and aspirin-antacid tablets each contained 0.32 g. aspirin.[1] The subjects took three tablets of a given preparation four times a day for eight days, followed each time by about 120 ml. of water. The different tablet preparations were taken in random order, with eight-day rest periods between the eight-day aspirin periods.

[1] Provided by Bristol-Myers Products, Hillside, N. J.

RESULTS AND DISCUSSION

The physicochemical characteristics of the regular aspirin and aspirin-antacid tablet preparations are summarized in Table I. The presence of antacid resulted in a considerably higher pH in the microenvironment of the aspirin particles, as reflected by the "paste pH" (5), when compared to that of regular aspirin tablets. The average daily blood losses (ADBL) during control periods and during periods of aspirin and aspirin-antacid administration, respectively, are shown in Tables II and III for each subject. The average data, together with those of a previous study (2), are summarized in Table IV. Shown also in Table IV are the results of the absorption study of the various preparations. A statistical analysis of the results of the bleeding studies is presented in Table V. Of the three regular aspirin tablet preparations tested (*B*, *C*, and *E* in Table IV), only *C* was absorbed at a rate similar to those of the two aspirin-antacid tablet preparations. Since the latter were very similar in their physicochemical (Table I) and absorption (Table IV) properties, their bleeding data were combined. This permitted a comparison of the ADBL of twelve subjects taking regular aspirin tablets with the ADBL of another twelve subjects taking aspirin-antacid tablets. The ADBL of 2.4 ml. in the aspirin-antacid group is significantly less ($p < 0.01$) than the ADBL of 4.7 ml. in the regular aspirin group. These results support the supposition that the addition of antacids to aspirin tablets can reduce aspirin-induced gastrointestinal bleeding by increasing the rate of dissolution of aspirin *in vivo* and thereby reducing the contact time between aspirin particles and the gastrointestinal mucosa. Additional studies, using

Table V—Significance of Differences in Gastrointestinal Bleeding Produced by Different Aspirin Tablet Preparations and During Control Periods

Comparison[a]	No. of Subjects	"*t*" Value[b]	Statistical Significance[c]
E vs. D	12	3.76*	+
F-I vs. D-I	6	2.38*	—
F-II vs. D-II	6	4.09*	+
E-I vs. F-I	6	1.22*	—
E-II vs. F-II	6	1.47*	—
E vs. F	12	1.83*	—
A vs. D	12	0.43	—
B vs. E	12	0.22	—
B vs. F	12	1.71	—
C vs. E	12	1.09	—
C vs. F	12	3.05	+

[a] Code designations as listed in Table IV. Comparisons based on total daily blood loss. *F* represents combined data for *F-I* and *F-II*. [b] Asterisk indicates paired comparisons. [c] + designates $p < 0.05$.

a cross-over design with a larger number of subjects and a single aspirin-antacid preparation, will be needed to permit more definitive conclusions. It is significant however that the more rapidly absorbed aspirin preparations *F-I* and *F-II* definitely do not cause more bleeding than the more slowly absorbed Preparation *E*. It therefore appears feasible to design aspirin tablet preparations with rapid drug release characteristics and relatively low gastrointestinal bleeding liability.

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Comparative Study of Two Antidandruff Preparations

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Abstract □ The relative antidandruff efficacy of a commercially available 2% zinc pyrithione shampoo, a 2.5% selenium sulfide suspension, and an unmedicated control shampoo was measured using a well-tested visual technique. The zinc pyrithione shampoo and the selenium sulfide suspension were found to be equally effective, both being significantly more effective than the control shampoo. A supplemental evaluation of the effects of the test products on scalp oiliness is also reported.

Keyphrases □ Antidandruff shampoos—effectiveness testing □ Zinc pyrithione, selenium sulfide—activity comparison

The question of whether dandruff is a mild form of seborrheic dermatitis, and thus a potential medical problem, or is just a deviation from a normal process of desquamation and thus a strictly cosmetic problem, remains open. In any event, the interest in dandruff seems clear from the many papers on the subject that have been published over the years (1–8).

A variety of agents have been used for the treatment of dandruff. Among these are sulfur, salicylic acid, hexachlorophene, tar, and quaternary ammonium compounds. One of the most popular remedies, in medical circles, has been a suspension of selenium sulfide (9). A relative newcomer, and a compound that has shown considerable promise, is zinc pyrithione.[1]

A clinical test of zinc pyrithione in a hairdressing vehicle has demonstrated that it is effective in the treatment of dandruff (10), and its safety in a shampoo has been documented (11). There has not been heretofore, however, any published clinical evidence that zinc pyrithione is effective in a shampoo.

This paper presents the results obtained in a controlled clinical study with the zinc pyrithione shampoo, using a visual grading method that has been developed during considerable experience in such testing. The purpose of the study was to determine whether the zinc pyrithione shampoo, offering some advantages in availability and convenience of use, provided dandruff control comparable to that offered by a selenium sulfide suspension.

MATERIALS AND METHODS

Three products were evaluated in the study: a commercially available zinc pyrithione shampoo[2] with an approximate composition shown in Formula I; a placebo shampoo, identical to the zinc pyrithione shampoo except for the omission of zinc pyrithione; a commercially available selenium sulfide suspension[3] with an approximate composition, as previously reported (12), shown in Formula II.

Formula I

	%
Zinc pyrithione	2.0
Surfactant	20.0
Foam builder	4.0
Thickeners	1.2
Perfume, color, stabilizer	2.0
Water	*q.s.* 100.0

Formula II

	%
Selenium sulfide	2.5
Surfactant	17.0
Inert and stabilizing ingredients	5.2
Water	*q.s.* 100.0

All three were packaged in identical containers.

Label instructions for the first two products called for use as any regular shampoo. Label instructions for the selenium sulfide suspension called for washing the hair with bland soap, rinsing, massaging the suspension into the scalp, letting it remain there for 5 min., and rinsing.

The testing procedure incorporated the following features:

1. The products were tested on comparable groups to which

[1] Zinc 2-pyridinethiol-1-oxide.

[2] Head & Shoulders Shampoo.

[3] Selsun.