Aspirin-Induced Occult Gastrointestinal Blood Loss: Local *versus* Systemic Effects

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Abstract □ The purpose of this study was to determine if occult gastrointestinal blood loss produced by therapeutic doses of aspirin in man is a local or systemic effect. The daily oral administration of from 3.9 to 5.2 g. aspirin in tablets for 8 days increased the average daily blood loss from 0.3 to 6.4 ml. in nine normal subjects. Intravenous administration of from 2.7 to 3.4 g. aspirin as the sodium salt per day for 3 days to the same subjects caused no measurable gastrointestinal blood loss above control values. The average bleeding time increased from a control value of 2.6 to 4.5 min. during oral aspirin administration and to 4.1 min. during intravenous administration of the drug. The absence of gastrointestinal bleeding due to intravenous aspirin and the similarity in the degree of prolongation of bleeding time by both oral and intravenous aspirin indicate that gastrointestinal bleeding is a local effect of the drug and is not related to changes in the bleeding time.

Keyphrases □ Aspirin—induced gastrointestinal blood loss, local *versus* systemic effects □ Gastrointestinal bleeding—aspirin-induced, local, systemic effects

The mechanism of aspirin-induced gastrointestinal blood loss has been the subject of considerable discussion. Some investigators believe that it is a local[1] effect (1, 2), while others consider it due to a systemic action of aspirin (3, 4). It has been suggested that the prolongation of bleeding time produced by aspirin may possibly play a role in the causation of gastrointestinal blood loss (5). The study described here was initiated for the purpose of assessing the degree of gastrointestinal blood loss caused by the relatively large oral doses of aspirin used for the relief of rheumatism and arthritis, and to compare this with that produced by intravenous aspirin. Bleeding times were determined during a control period and during oral and intravenous aspirin administration to establish the possible relationship between this effect and gastrointestinal blood loss.

METHODS

Nine healthy, ambulatory subjects (sex, age, and weight listed in Table I) had their red blood cells labeled with ^{51}Cr as described in a previous paper (6). They collected their stools over a 35-day period for the determination of fecal blood loss (6). The first 8 days served as a control period. From 3.9 to 5.2 g. aspirin as 0.3-g. tablets (Bayer) were taken daily, in four equal doses, for the next 8 days. After a rest period of 11 days, 2.7–3.4 g. aspirin as sodium acetylsalicylate dissolved in 250 ml. of normal saline was injected intravenously at a constant rate over a 1–2-hr. period each day for 3 days.

Bleeding times were obtained on the last 2 days of the control and oral aspirin periods and on each day of the intravenous aspirin period at the end of the injection. At least six stab wounds (three on each arm) were made on each day, and the reported bleeding times are averages of 12 to 36 individual determinations. The stab wounds were made with a disposable lancet (Dade Hemolet) with a blade 4 mm. long and 1.4 mm. wide at the base, which was attached to a specially modified spring-type automatic lancet holder.

[1] In this discussion, "local effect" refers to the topical exposure of the gastrointestinal mucosa to ingested aspirin.

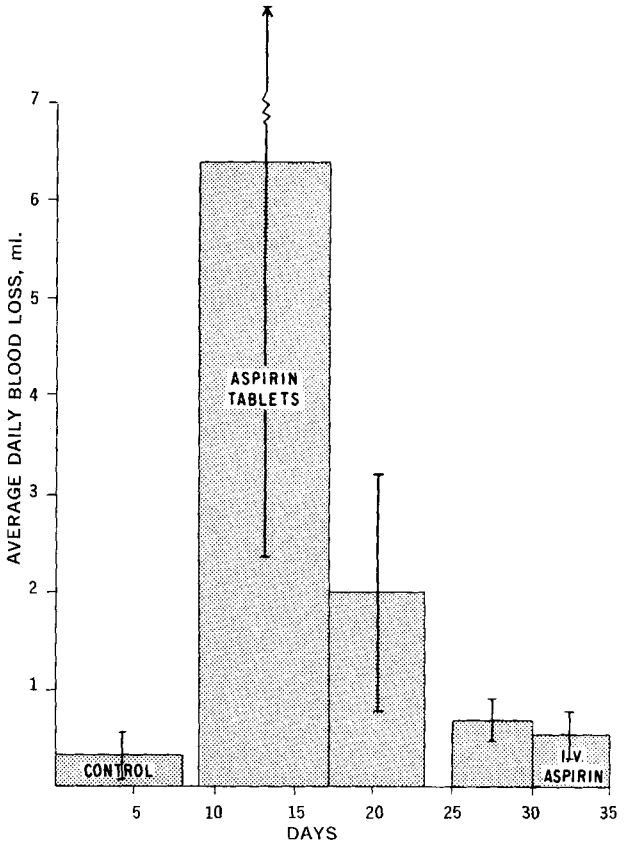

Figure 1—*Average daily occult gastrointestinal blood loss in nine normal subjects during a control period, during oral administration of 3.9–5.2 g. aspirin in tablet form per day, during postdrug periods, and while receiving 2.7–3.4 g. aspirin intravenously for 3 days. Vertical bars are standard deviations.*

RESULTS

The results of the study are summarized in Table I. Oral administration of aspirin caused a pronounced and statistically significant increase in average daily blood loss (ADBL), which persisted for at least 6 days after the last day of drug ingestion. The total average blood loss due to aspirin was 59 ml. above control values, based on the bleeding observed from the 10th to the 23rd day of the study. One individual lost 129 ml. of blood during this period, or 117 ml. in excess of the control value. Intravenous administration of aspirin did not cause any measurable bleeding under the experimental conditions. There was no statistically significant difference (by paired *t* test) in the ADBL during the intravenous aspirin period and the initial control period. The time course of ADBL in the various control, treatment, and rest periods is shown in Fig. 1.

The average bleeding time was 2.6 min. in the control period. There was a statistically significant ($p < 0.01$) increase in bleeding time to 4.5 min. during oral aspirin administration and to 4.1 min. in the period when aspirin was given intravenously (Table I).

Table I—Effect of Aspirin Tablets and Intravenous Aspirin on Gastrointestinal Blood Loss and Bleeding Time in Man

	Subject									Mean	
	G.P.	R.F.	A.T.	R.N.	C.D.	J.E.	M.G.	M.B.	T.F.	Value	*SD*
Sex	M	M	M	M	F	F	M	M	F		
Weight, kg.	66	71	73	77	65	52	77	66	57		
Age, yr.	26	24	24	19	19	20	22	24	24		
Daily dose, oral aspirin, g.	4.5	5.2	3.9	5.2	4.5	3.9	5.2	4.5	3.9		
Daily dose, i.v. aspirin, g.	2.7	2.7	2.7	2.7	3.0	2.7	3.4	3.4	3.0		
ADBL,[a] ml.											
1st–8th day (control)	0.2	0.3	0.3	0.35	0.3	0.3	0.85	0.2	0.3	0.3	0.2
10th–17th day (aspirin tablets)	9.2	8.2	3.7	8.1	3.4	3.2	14.6	5.4	1.7	6.4	4.0
18th–23rd day	1.4	2.2	2.0	2.3	0.9	3.2	2.0	3.7	0.25	2.0	1.1
26th–30th day	1.1	1.0	0.5	0.6	0.5	0.5	0.9	0.5	0.8	0.7	0.2
31st–35th day (i.v. aspirin)	0.7	0.6	0.7	0.5	0.3	0.5	0.4	0.9	0.4	0.6	0.2
				Average Bleeding Time, min.							
Control	1.9	2.3	3.1	2.9	3.3	2.9	2.4	2.0	2.8	2.6	0.5
Aspirin tablets	2.7	4.5	5.7	4.6	5.3	5.5	3.1	4.9	4.4	4.5	1.0
i.v. Aspirin	3.2	3.3	5.0	4.0	6.0	4.5	4.0	3.6	3.6	4.1	0.9

[a] Average daily blood loss.

DISCUSSION

The relatively large oral doses of aspirin tablets employed in this study caused appreciable gastrointestinal blood loss. The ADBL of 6.4 ml. observed in this study during daily administration of 4.5 g. aspirin on the average may be compared to an average of 2.3 ml. in 15 subjects who received daily doses of only 2.6 g. of the same aspirin tablets in a previous study (7). Gastrointestinal bleeding due to aspirin is, therefore, of increasing significance when relatively high doses of the drug are used.

No bleeding was observed during intravenous administration of aspirin to the subjects in this study, although the same or larger doses caused significant gastrointestinal blood loss when given orally (7). The period of oral administration of aspirin (8 days) was considerably longer than the period of intravenous administration (3 days). However, comparison of the ADBL of the nine subjects during the first 3 days of oral administration of aspirin (5.7 ml.) with that during the 3 days of intravenous administration (0.45 ml.) yields essentially the same results as those listed in Table I for the longer time periods. Both sets of data show statistically significant ($p < 0.01$ by paired t test) blood loss during oral administration of aspirin and no evidence of aspirin-induced bleeding when the drug was given intravenously. Due to technical problems, intravenous aspirin was always given after a period of oral aspirin administration rather than in a crossover fashion, but it has already been shown (6, 7) that the bleeding response to aspirin is not affected by previous aspirin administration when followed by an 8-day rest period.

The results of this study are consistent with those of Anderson (1) and Davison *et al.* (2) who did not detect any gastric erosions or bleeding after parenteral administration of aspirin to guinea pigs, rabbits, and dogs in doses that caused significant gastric damage when given by the oral route. Simultaneously with the preliminary report of this study (8), Cooke and Goulston (9) recently reported that intravenous infusion of 1 g. aspirin twice daily for 3 days did not increase the fecal blood loss in 15 healthy human subjects above control levels. However, they did not challenge their subjects with oral aspirin.

The paper by Grossman *et al.* (3) has been cited frequently in support of the contention that aspirin-induced gastrointestinal blood loss in man is a systemic effect. These investigators reported a barely statistically significant increase in ADBL from intravenous aspirin administration, but it should be noted that most of the subjects had peptic ulcer; some had bled within 2 weeks of the study, and much more bleeding was observed when the same dose of aspirin was administered orally (2.1 ml. *versus* 0.8 ml./day in excess of control values). There has been a number of reports of gastric hemorrhage following parenteral administration of aspirin to rats (10, 11) and cats (12), but the doses used were massive (300 to 1300 mg./kg.) and often lethal. It is unrealistic to extrapolate the results obtained under these extreme conditions to the therapeutic doses used in man. Brodie and Chase (13) recently reported a statistically significant increase in the incidence of gastric hemorrhage in rats given 64 mg. aspirin/kg., either orally or intraperitoneally. They noted, however, that hemorrhage was much less severe and the lesions were smaller when the drug was given intraperitoneally. Since the serosal side of the stomach is exposed directly to aspirin particles when the drug suspension is injected intraperitoneally, this effect could well have been a local one.

The prolongation of bleeding time during aspirin administration observed in this study is in agreement with the reports of other investigators (5). The prolonged bleeding time during intravenous aspirin administration was not a carryover from the oral aspirin period, since the bleeding times determined in several of the subjects just prior to the first intravenous dose of aspirin was similar to their control times. The rigid standardization of the stab wound (due to the use of an automatic lancet) and the large number of determinations accounted for the very small variability of the bleeding times.

The results of this study show that gastrointestinal blood loss in normal human subjects receiving therapeutic doses of aspirin is a local effect and that it is not related to the prolongation of bleeding time produced by aspirin. It is, therefore, reasonable that the gastrointestinal bleeding liability of aspirin preparations can be reduced or even eliminated (7, 14, 15) by appropriate pharmaceutical formulation designs. Such preparations would be particularly important for the treatment of rheumatoid arthritis, which usually requires relatively high doses of aspirin. Unfortunately, none of the presently available preparations is ideally suitable for this purpose, mainly because of the high sodium content or limited buffer capacity. The feasibility of developing more suitable preparations for this purpose is now being explored.

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Effect of Micelle Formation on Optical Rotatory Dispersion of β-D-Octyl Glucoside

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Abstract □ The optical rotatory dispersion of a nonionic surfactant, β-D-octyl glucoside, has been investigated in aqueous solutions in the UV region. The rotatory dispersion curves at any concentration can be represented by a one-term Drude equation. The specific rotation at any wavelength shows an increase at the CMC, which can be determined reliably from this change in specific rotation. The rotatory dispersion curve for the surfactant in micellized form has been derived and compared with that of the nonmicellized surfactant below the CMC. The change is small and can be ascribed to a "medium" effect, arising from the difference in the local refractive index at the micelle surface, as compared to the bulk solvent. This interpretation is compatible with the currently accepted ideas on the fluid nature of the micelle core and suggests a lack of any conformational restraint at the micellar interface.

Keyphrases □ Optical rotatory dispersion, β-D-octyl glucoside—micelle formation effect □ β-D-Octyl glucoside—optical rotatory dispersion, micelle formation effect □ Micelle formation, effect—optical rotatory dispersion, β-D-octyl glucoside

Many chemical and biochemical reactions and interactions of interest occur at interfaces, *e.g.*, monolayers, micelles, enzymes, or membranes. The local molecular environment at an interface and the presence of an asymmetry and other peculiarities in dielectric properties (1) are factors of considerable importance in understanding the properties of molecules at interfaces. It has been pointed out recently that for studying many such interactions, the interface between a micelle and the solution provides a convenient locus whose composition is capable of a considerable controlled variation (2, 3). The use of optically active surfactant monomers or solubilized molecules offers the possibility of using optical activity as a probe for studying properties of interfaces and of understanding the effect of the interface composition on the optical activity itself. The present paper reports what appears to be the first such study on a simple model surfactant system, β-D-octyl glucoside.

β-D-Octyl glucoside has a CMC in aqueous solution of 0.024–0.025 *M* at 25° (4, 5). The micelles probably contain about 30 monomers (6), the hydrocarbon chains forming a spheroidal core. The glucoside head groups presumably remain exposed to water both in the monomeric and micellar forms. This, by itself, would suggest that there should be no change in their optical activity. In fact, however, the packing of the chains produces a high effective concentration of the head groups in the interfacial layer (2), which interact strongly enough with each other to counter the micelle-forming tendency of the aliphatic chain rather substantially. This is apparent from the following comparison.

Recently the CMC of a hypothetical octyl chain, unencumbered by any head group, was estimated to be about 3×10^{-3} *M* (3). The CMC of octyl glucoside is higher by a factor of about 8. The head group self-interaction thus makes the standard free energy of micelle formation for octyl glucoside more positive by $kT \ln 8$ or about $2kT$'s per monomer, where k is the Boltzmann constant and T the absolute temperature (3). The glucoside groups at the micelle surface are thus in a considerably different local environment when compared to the free monomers.

EXPERIMENTAL

Materials—The octanol used was a Baker analyzed reagent, which was purified further by vacuum distillation, the middle one-third portion being collected.

β-D-Octyl Glucoside—Glucose, on acetylation followed by bromination (7), yielded acetobromoglucose, m.p. 89°. The bromo compound was reacted with octanol in dry absolute ether in the presence of silver oxide to give β-tetraacetyl octyl glucoside, m.p. 63–64°. After deacetylation in sodium methylate solutions, β-D-octyl glucoside was obtained. It was recrystallized twice from ethyl acetate, washed with Skelly-A, and dried under vacuum. The compound melts over a wide range, 65–99° (8). The intermediate compounds were purified by recrystallization before proceeding to the next step of the preparation.

Anal.—Calcd. for C, 57.5; H, 9.7. Found: C, 57.8; H, 9.5.

Apparatus and Experimental Procedure—The optical rotatory dispersion (ORD) measurements were carried out in a Cary model 60 spectropolarimeter. The cell compartment was thermostated at 25 ± 0.2°. Five-centimeter cells were used. All solutions were optically clear, and double-distilled water was used. The ORD measurements were made in the 250–370-mμ region.

RESULTS

Figure 1 shows the variation of the observed rotation at 320 mμ as a function of concentration. To magnify the small differences observed, a deviation plot is presented. The data show the usual curvature near the CMC. If the CMC region is excluded, the data