Effect of Anticoagulant Therapy upon Aspirin-Induced Gastrointestinal Bleeding

By Richard M. Watson, M.D., and Richard N. Pierson, Jr., M.D.

Aspirin has been shown to cause gastrointestinal bleeding. Although the blood loss associated with the relatively small dosage that is customarily used is slight (usually well below 10 ml. per day), there are some situations in which the safety of aspirin may be questioned. Such a situation is the administration of aspirin to patients who are simultaneously receiving anticoagulant therapy. Some authors have, in fact, recommended that such patients should not use salicylates in any form. In view of the increasing number of patients who are receiving anticoagulants on a long-term basis, and the ubiquitous use of aspirin, it is important to know whether significant increase in gastrointestinal blood loss occurs in the presence of this combination of agents. The present study was designed to evaluate the safety of salicylate ingestion in combination with anticoagulation, under controlled conditions. In addition, the possible effect of salicylate ingestion on the dosage of anticoagulant needed to produce satisfactory levels of hypoprothrombinemia was studied.

Method

The group under study consisted of sixteen men and nine women who were patients on the medical wards of St. Luke's Hospital. These patients, whose ages ranged from 31 to 85, were receiving acenocoumarin* to prevent complications of coronary artery disease, thrombophlebitis, and atrial fibrillation.

Erythrocytes were labeled with sodium radiochromate and reinjected according to a previously described method, and fecal blood content was calculated from the ratio of fecal: blood radioactivity. Prothrombin time was determined by the Link-Shapiro modification of Quick's method. When stable acenocoumarin dosage and prothrombin activity levels were attained, a 3-day quantitative stool specimen was collected and measured for blood content, and the result was considered a control value. Each patient was then given aspirin, 600 mg. four times daily. After a 3-day interval to allow for intestinal transit time, a second stool specimen was similarly obtained and measured. (In a group of 131 normal volunteers, who were previously studied by the same technic, the mean daily control fecal blood content was 0.5 ± 0.4 ml. whereas that during periods of aspirin administration of the same dosage, was 4.7 ± 4.1 ml.)

In order to determine the effect of aspirin upon prothrombin activity, the average daily maintenance dosage of acenocoumarin was calculated both before and during the week in which aspirin was given.

Results

Fecal Blood Content

Results were obtained for fecal blood loss in 20 patients for control periods, and for 188 patients for aspirin periods. Seventeen patients completed both aspirin and control periods. The observations are summarized in figure 1, in which two groups of subjects are compared: the group receiving anticoagulants during both aspirin and control periods, and a group of 131 normal volunteers who were similarly evaluated during both aspirin and control periods. The average daily blood loss in the anticoagulant group was 1.1 ± 1.0 ml. (range 0.1 to 3.2 ml.) during the control period, and 4.7 ± 3.4 ml. (range 0.8 to 13.0) during the aspirin period. Corresponding figures for the volunteer group were 0.5 ± 0.4 (range 0 to 1.9) and 4.7 ± 4.1 (range 0.5 to 85) ml. respectively. In the volunteer group, 73 per cent of the subjects had a daily fecal blood loss in excess of 0.1 ml.

\[ \text{S.D.} = \sqrt{\frac{(x - \bar{x})^2}{n - 1}} \]
1.5 ml., or 2 1/2 standard deviations above their own mean control level during aspirin period. Of the subjects receiving the anticoagulant, 76 per cent showed a daily blood loss in excess of 1.5 ml. during the aspirin periods. Since the control level of the latter group is higher, however, the establishment of an acceptable "significant" increase in rate of bleeding is correspondingly higher. Thus, 67 per cent of the subjects receiving anticoagulants had a daily blood loss during the aspirin period that was 2 1/2 standard deviations, or more, above their own control level.

Alternations in Anticoagulant Dosage

Seventeen patients were observed for a sufficient length of time both with and without aspirin to calculate average daily maintenance dosages of acenocoumarin (fig. 2). Eleven of these patients required a reduction in daily acenocoumarin dosage of 0.5 mg. or more. These patients were maintained on a daily average of 3.1 mg. of acenocoumarin during the control period and 2.2 mg. during the aspirin period. Five other patients required a dosage reduction of less than 0.5 mg.; this was not considered significant because of the inaccuracy of dividing the 4-mg. tablet. Only one patient had an increase in maintenance dosage while taking aspirin, and this increment was only 0.5 mg. The daily blood loss in those patients in whom aspirin seemed to have a hypoprothrombinemic effect was no greater than in the others. Thus, there was no correlation between bleeding tendency and aspirin-induced hypoprothrombinemia.

Complications

Anticoagulant therapy had to be discontinued in four patients during the course of the study. One of the patients experienced frequent episodes of epistaxis while taking aspirin, but he had previously shown an elevation in fecal blood content (7.2 ml. per day) during the control period. Another patient had a sudden episode of rectal bleeding during which 140 ml. of blood were lost; the source of this bleeding was believed to be hemorrhoidal. A third patient developed gross hematuria before aspirin was started. The fourth had an episode of upper gastrointestinal bleeding, also before aspirin was started. Thus, aspirin could not be inerminated in any of these complications. These patients are not included in table 1.

Discussion

A variety of mechanisms have been proposed in order to explain the bleeding that occurs with the ingestion of aspirin:

1. Hypoprothrombinemia. Link and co-workers' first showed that salicylic acid could produce hypoprothrombinemia in rats, and actually postulated that degradation to salicylic acid was the basis of the prothrombin-depressing effect of bishydroxycoumarin. More recently, evidence has been produced to challenge the latter point.2, 7

Rapoport et al., Meyer and Howard,9 and Shapiro et al.10 subsequently described a similar hypoprothrombinemic effect, both with aspirin and sodium salicylate, upon human beings. Although clinical reports have described hematemeses following aspirin use to hypoprothrombinemia,11, 12 the prothrombin levels quoted are not sufficiently low to explain such bleeding. The present study suggests that hypoprothrombinemia is not a significant factor in salicylate bleeding.

2. Gastritis. Dowthwaita and Lintott13 have reported gastroscopic observations on subjects who had previously swallowed aspirin tablets, and described a generalized gastritis, in
Acenocoumarin requirements during control (A) and aspirin (B) periods.

addition to small areas of hyperemia surrounding undissolved particles of aspirin. They also reported submucous hemorrhages, as well as actual bleeding points. Muir and Cossar14 examined the stomachs of patients who had received aspirin prior to gastrectomy, and described similar changes, with the additional finding of minute ulcerations beneath the undissolved particles.

3. Exacerbation of peptic ulceration. There have been reports14-16 of both ulcer symptoms and of gastrointestinal bleeding appearing after aspirin ingestion. The manner in which aspirin might activate peptic disease is not clear, but it has been suggested that this may be due to the action of an irritant upon the chronic gastritis that frequently exists in the individual with peptic disease.14 Of particular interest in these reports is the tendency toward repetition of gastric complications (both ulcer symptoms and bleeding) following the use of aspirin by such individuals.

4. Capillary fragility. This has been described as a factor in the bleeding of salicylate toxicity because of the appearance of a positive Rumpel-Leeds test in the presence of an otherwise intact clotting mechanism (other than mild hypoprothrombinemia).17 This has also been shown in a pathologic study of two patients who died of hemorrhagic complications following heavy doses of salicylates, in whom numerous microscopic petechiae were found.11

5. Thrombocytopenic purpura. Although this has been reported to occur following the use of aspirin, it is very rare.18 The relevant effects that have been most consistently observed with small analgesic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex and Age</th>
<th>Diagnosis</th>
<th>Blood loss ml./Day</th>
<th>Average daily dose acenocoumarin (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 AP</td>
<td>M 50</td>
<td>MI</td>
<td>C 2.6</td>
<td>3.4</td>
</tr>
<tr>
<td>2 IR</td>
<td>M 62</td>
<td>MI</td>
<td>C 0</td>
<td>4.0</td>
</tr>
<tr>
<td>3 EG</td>
<td>M 57</td>
<td>MI</td>
<td>C 0.4</td>
<td>8.5</td>
</tr>
<tr>
<td>4 MQ</td>
<td>F 75</td>
<td>MI</td>
<td>C 2.0</td>
<td>3.6</td>
</tr>
<tr>
<td>5 AG</td>
<td>M 76</td>
<td>MI</td>
<td>C 0.2</td>
<td>3.0</td>
</tr>
<tr>
<td>6 JC</td>
<td>F 70</td>
<td>MI</td>
<td>C 0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>7 DU</td>
<td>M 31</td>
<td>RHD, AF</td>
<td>C 0.9</td>
<td>3.4</td>
</tr>
<tr>
<td>8 JC</td>
<td>M 45</td>
<td>Angina</td>
<td>C 0.1</td>
<td>1.4</td>
</tr>
<tr>
<td>9 CG</td>
<td>F 50</td>
<td>RHD, AF</td>
<td>C 0.2</td>
<td>4.3</td>
</tr>
<tr>
<td>10 ML</td>
<td>M 78</td>
<td>MI</td>
<td>C —</td>
<td>4.0</td>
</tr>
<tr>
<td>11 TC</td>
<td>M 59</td>
<td>MI</td>
<td>C 3.2</td>
<td>4.0</td>
</tr>
<tr>
<td>12 AM</td>
<td>M 69</td>
<td>AF</td>
<td>C 1.5</td>
<td>5.5</td>
</tr>
<tr>
<td>13 PM</td>
<td>M 56</td>
<td>MI</td>
<td>C 0.3</td>
<td>1.9</td>
</tr>
<tr>
<td>14 AG</td>
<td>M 43</td>
<td>MI</td>
<td>C 0.7</td>
<td>3.0</td>
</tr>
<tr>
<td>15 JM</td>
<td>F 46</td>
<td>MI</td>
<td>C 0.3</td>
<td>6.0</td>
</tr>
<tr>
<td>16 IB</td>
<td>F 51</td>
<td>MI</td>
<td>C 2.6</td>
<td>7.0</td>
</tr>
<tr>
<td>17 JA</td>
<td>F 68</td>
<td>MI</td>
<td>C 2.8</td>
<td>6.0</td>
</tr>
<tr>
<td>18 CM</td>
<td>F 35</td>
<td>Thr.</td>
<td>C 1.5</td>
<td>—</td>
</tr>
<tr>
<td>19 JS</td>
<td>M 43</td>
<td>MI</td>
<td>C 6.0</td>
<td>—</td>
</tr>
<tr>
<td>20 CS</td>
<td>M 47</td>
<td>MI</td>
<td>C 0.3</td>
<td>—</td>
</tr>
<tr>
<td>21 MS</td>
<td>M 41</td>
<td>Angina</td>
<td>C 0.2</td>
<td>—</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; MI, myocardial infarction; RHD, rheumatic heart disease; Thr., thrombophlebitis; C, control period; A, aspirin period.
doses of aspirin are those of gastritis13, 14 and
a lowered prothrombin activity.11 In the pres-
ent study, and in a previous study of normal
volunteers,19 lowered prothrombin activity
was not correlated with daily blood loss. The
results suggest, however, that an already low
prothrombin level might, in an occasional
patient, be further depressed to a dangerous
level. Such an incident was not observed in
this group of patients because prothrombin
determinations were performed every day,
and appropriate dose adjustments were made.
Since the rate of bleeding did not appear to
be influenced by anticoagulation, it would be
tempting to deny any hazard in the use of
aspirin. More extensive bleeding has been ob-
erved, however, in 5 to 10 per cent of normal
volunteers studied in this laboratory (up to
85 ml. per day). Since no such persons were
found in this study group, it is impossible
to predict the influence of anticoagulation
upon “susceptible” persons with aspirin-
induced bleeding of this magnitude.

Summary and Conclusions

A group of patients receiving oral anti-
coagulants was studied during control periods
and periods during which aspirin was admin-
istered, with respect to rate of blood loss via
the gastrointestinal tract. These patients did
not bleed at a significantly greater rate than
did previously studied normal volunteers,
when taking aspirin; however, the anticoagu-
lant group showed a slightly higher blood loss
during the control period.
The majority of patients showed a slight
though detectable decrease in prothrombin
activity, as evidenced by a reduction in anti-
cogulant dosage, during the aspirin period.
The results of this study indicate that
aspirin, in a dose of 600 mg. four times daily,
rendered no apparent increased hazard of
gastrointestinal bleeding in the small group
of subjects without evident gastrointestinal
disease studied. Patients who must take
aspirin continuously, however, may require a
reduction in anticoagulant maintenance dosage.

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