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 receivingacenocoumarin* 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

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\text{S.D.} = \sqrt{\frac{(x - \bar{x})^2}{n - 1}}
\]
1.5 ml., or 2½ 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 2½ standard deviations, or more, above their own control level.

**Alterations 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-workers⁶ 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 ofbishydroxycoumarin. More recently, evidence has been produced to challenge the latter point.²⁷

Rapoport et al.,⁸ 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 ascribed hematemesis 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.** Douthwaite and Lintott¹³ have reported gastroscopic observations on subjects who had previously swallowed aspirin tablets, and described a generalized gastritis, in

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GASTROINTESTINAL BLEEDING AFTER ASPIRIN

Figure 2
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 Cossar 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 reports 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. 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). 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.

5. Thrombocytopenic purpura. Although this has been reported to occur following the use of aspirin, it is very rare.

The relevant effects that have been most consistently observed with small analgesic

Table 1
Summary of Patients and Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex and age</th>
<th>Diagnosis</th>
<th>Blood loss ml./Day</th>
<th>Average daily dose of 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>A 2.2</td>
<td>3.0</td>
</tr>
<tr>
<td>4 MQ</td>
<td>F 75</td>
<td>MI</td>
<td>C 0.4</td>
<td>8.5</td>
</tr>
<tr>
<td>5 AG</td>
<td>M 76</td>
<td>MI</td>
<td>A 1.3</td>
<td>9.0</td>
</tr>
<tr>
<td>6 JC</td>
<td>F 70</td>
<td>MI</td>
<td>A 5.6</td>
<td>2.4</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 0.2</td>
<td>3.0</td>
</tr>
<tr>
<td>9 CG</td>
<td>F 50</td>
<td>RHD, AF</td>
<td>A 3.4</td>
<td>1.2</td>
</tr>
<tr>
<td>10 ML</td>
<td>M 78</td>
<td>MI</td>
<td>C 0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>11 TC</td>
<td>M 59</td>
<td>MI</td>
<td>A 3.2</td>
<td>4.0</td>
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<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>A 2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>15 JM</td>
<td>F 46</td>
<td>MI</td>
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<td>2.0</td>
</tr>
<tr>
<td>16 IB</td>
<td>F 51</td>
<td>MI</td>
<td>A 7.4</td>
<td>5.3</td>
</tr>
<tr>
<td>17 JA</td>
<td>F 68</td>
<td>MI</td>
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<td>6.0</td>
</tr>
<tr>
<td>18 CM</td>
<td>F 35</td>
<td>Thr.</td>
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<td>6.0</td>
</tr>
<tr>
<td>19 JS</td>
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<td>MI</td>
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<tr>
<td>20 CS</td>
<td>M 47</td>
<td>MI</td>
<td>C 6.0</td>
<td>—</td>
</tr>
<tr>
<td>21 MS</td>
<td>M 41</td>
<td>Angina</td>
<td>A 5.3</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C 0.2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A 9.6</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 present 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 observed, 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 anticoagulants was studied during control periods and periods during which aspirin was administered, 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 anticoagulant 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 anticoagulant 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.

References

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