The Risk of Interrupting Long-Term Anticoagulant Treatment
A Rebound Hypercoagulable State Following Hemorrhage

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LONG-TERM anticoagulation is an accepted mode of treatment for prevention of emboli from fibrillating hearts, thrombotic occlusions in arteriosclerotic disorders, and pulmonary emboli in phlebitis. The degree of success in coronary artery disease is somewhat disappointing because it does not completely eradicate death from this cause although the incidence of thrombotic complications is clearly reduced.1-3 These results, of course, suggest that intravascular coagulation plays a secondary although important role rather than a primary role as postulated by Duguid.4 The experience acquired during the past 15 years based on laboratory research and clinical observations has led to the establishment of a more or less safe technic of anticoagulant administration. In experienced hands the benefits derived from the use of anticoagulant drugs in carefully selected cases outweighs the risk from bleeding complications due to these drugs. Besides bleeding, as a major complication it has also been noted that discontinuance of treatment for one reason or another carried with it a risk of recurrence of a thrombotic condition. This has been called the rebound phenomenon. In this paper the term "rebound" refers to such post-anticoagulant thrombosis.

Thus, Gosgriff5 in reporting on anticoagulant treatment in recurrent embolism of cardiac origin observed that of 17 patients who stopped treatment, 12 developed 14 embolic episodes. Eight of them happened within 4 weeks after stopping treatment, the other six between the third and twenty-third month. Further, Keyes, Drake, and Smith6 noted new infarcts in 14 of 28 patients who stopped anticoagulation during a period of 3 days to 20 months. There were six fatalities. Interruption of treatment in half of the instances was because of hemorrhage. Carter, McDevitt, Gatje, and Wright7 found a higher tendency to recurrent thromboembolism following discontinuation of anticoagulants within the first 6 weeks, particularly in those with a more pronounced tendency to recurrent thromboembolism or those with congestive heart failure. It is of interest that this incidence of recurrent thromboembolism was higher in the group that stopped anticoagulation than in the group that after a thromboembolic episode remained off anticoagulants. Results of a follow-up study of 293 patients who stopped anticoagulation "for various reasons including hemorrhage" are reported by Nichol et al.8 A total of 90 patients died of "heart attack"; 20 within the first month and 70 within the subsequent 4 years. In their "discontinued group" of 203 patients, Thomas, Scallen, and Savage9 noticed a high recurrence rate during the first year after stopping treatment. The longer the treatment the higher was the observed rate of recurrence after stopping. In 13 instances the treatment was discontinued because of bleeding. Of the total, six had a recurrence within the first year after stopping treatment, in four of whom it was fatal. Bjerklund10 did not notice...
an increase in the mortality rate as compared to the control group when patients stopped treatment after 3 to 5 years. Finally, Dinon and Vander Veer\textsuperscript{11} reported on 20 cases with recurrence of acute myocardial infarction within 4 weeks after stopping abruptly or relatively rapidly oral anticoagulation.

These observations suggest that there may be a hypercoagulable state after interrupting long-term anticoagulation. Since it is inevitable that some patients will have to stop treatment for one reason or another, such as bleeding, surgical procedures, other illnesses or some other reason, and thereby expose themselves to a potential risk, this problem was investigated.

**Material and Methods**

From a consecutive series of 310 patients on long-term anticoagulant treatment with either phenindione or warfarin all patients were collected who had interrupted treatment for any reason and were divided into three groups. Group A consisted of those whose treatment was interrupted because of bleeding. Included were all instances in which the anticoagulant was stopped for 3 days or more, vitamin K\textsubscript{1} in a dose large enough to return the prothrombin time to normal was given, or the patient received a transfusion. Excluded were instances in which the anticoagulant was stopped for 1 or 2 days only. There were 45 instances in 43 patients, two patients having two episodes of bleeding.

Group B consisted of all those who gave up treatment permanently for one reason or another before the end of the period for which they were being treated. The reasons for stopping were either the patient discontinuing of his own choice, treatment discontinued by another medical facility because of a second unrelated disease, an operation in which the conditions did not warrant continuation, patient moved away, was unreliable, or could not get transportation to the laboratory. There were 53 instances in 52 patients, one patient gave up treatment of her own accord twice, but resumed it after the first period of abstinence because of a complication and stopped again.

Group C consisted of all those who stopped treatment temporarily for any reasons other than bleeding. This was predominantly for surgical procedures. There were 38 instances in 28 patients, seven patients more than once because of repeated procedures, usually tooth extractions.

Thromboembolic complications were considered to have happened if the conditions seemed to jus-
LONG-TERM ANTICOAGULANT TREATMENT

Figure 1

Time intervals between interruption of anticoagulant treatment and appearance of a complication.

Details in regard to the composition of the three groups are shown in table 1. They were similar in age distribution, incidence of diabetes, and hypertension. There were a few more women in group B than in the other two groups. More patients were treated for peripheral emboli from the heart in group C and fewer patients were treated for coronary artery disease in group A. Thus, group C is a distinctly different group, but groups A and B are comparable. At least the differences are not sufficient to explain the results noted below.

Results

In group A there were 10 fatal and 10 nonfatal complications. Fourteen of the 20 complications happened within 4 weeks of stopping treatment. This was a distinct difference from groups B and C and suggested a rebound effect.

In group B there were seven fatal and eight nonfatal complications. Only one complication happened in the first 4 weeks, and this was nonfatal.

In group C there were only three complications, all of which were nonfatal. They consisted of an embolus to the leg in one patient with rheumatic heart disease 5 days after interruption of treatment for an appendectomy, coronary insufficiency in a patient 5 days after interruption for a tooth extraction, and transient cerebral vascular insufficiency in a patient 7 days after interruption of treatment because it was thought that the anticoagulant preparation might be producing a syndrome of dry mouth. From the observations in groups B and C it appeared that interruption of treatment for short periods of time could be accomplished without a great risk. Because of its different composition group C was dropped from further considera-
Table 2

Differences in Mortality and Total Complication Rates of Groups A and B* by Months of Exposure

<table>
<thead>
<tr>
<th>Month</th>
<th>Mortality rate</th>
<th>Total complication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>1</td>
<td>0.219</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.154</td>
<td>0.027</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.029</td>
</tr>
</tbody>
</table>

* Mortality rate was calculated as the ratio \( \frac{d_r}{O_r - \frac{1}{2}W_r} \) in which \( d_r \) = the number of deaths, \( O_r \) the number of cases exposed to the risk, and \( W_r \) = the number of cases withdrawn from observation because of loss to follow up. Those who resumed treatment during the month were subtracted from \( O_r \) of the subsequent month. The total complication rate was calculated in the same way except \( d_r = \) sum of the number of fatal plus the number of nonfatal complications. The standard error was calculated by the formula \( SE = \sqrt{\frac{d_r}{O_r - \frac{1}{2}W_r} \cdot \frac{d_r}{O_r - \frac{1}{2}W_r}} \)

The high incidence of complications occurring shortly after interruption because of bleeding suggested a real difference in this group (fig. 1). This was even more evident when the period of exposure was taken into account. Since the patients in group B were withdrawn permanently they were continuously exposed to a risk. On the other hand, in group A many of the patients were started on treatment again as soon as the bleeding problem was controlled. From the formula\(^12\) for calculating rates of survival and for survival without a complication for each month of exposure, it was observed that the difference in the mortality in the first month between group A and group B was sufficiently great to give a critical ratio of difference to standard error of 2.26 (\( p \) less than 0.05). If the same was calculated for both fatal and nonfatal complications, the critical ratio was 2.65 (\( p \) less than 0.01). After the first month there was no significant difference between the two groups (table 2).

The possibility was considered that a difference in the composition of the two groups might account for the results. It might be expected that the slight predominance of men in group A could bias this group toward an increased number of complications. It does not explain, however, why these should come any sooner. Moreover, group B was biased by having more patients with coronary artery disease in whom the chance of complication was greater and the prognosis consequently worse.

It is suggested that discontinuance of treatment early in the course of long-term anticoagulation might be accompanied by a higher complication rate than late discontinuance.\(^1\) The possibility that patients in group A interrupted treatment earlier than those in group B was examined. The results indicated to the contrary that patients in group A had been on treatment slightly longer than those in group B before interruption. Those who had complications showed the same duration of treatment as those who did not. This applied in both groups (table 3).

Since differences in the composition of the groups did not seem to explain adequately the early appearance of complications in group A, other explanations were sought. Administration of vitamin K\(_1\) might induce a return to a hypercoagulable state. Transfusions with banked blood might introduce thromboplastic substances analogous to the clot-promoting property of serum described by Wessler.\(^13\) Tissue ischemia secondary to blood loss might
initiate a series of events culminating in a thrombus formation. The role of these three factors was observed by comparison of complicated and uncomplicated patients in group A. There is some tendency toward complications in those who had ischemic symptoms such as chest pain or transient cerebral symptoms, as may be seen in table 4, but the numbers are too small to be of significance. There is no clear indication that vitamin K1 or transfusions should be withheld for fear of precipitating a thrombotic complication. There is overlap in the figures given because a single patient often fell into more than one category.

The complications showed no definite relation to the source of the bleeding (table 5). Even after relatively minor bleeding such as hematuria and a small hematoma, fatal complications were observed. The presence of associated conditions such as ulcer or diabetes was not associated with an observable difference in rate of complications, but the figures are too small to be of significance.

**Discussion**

Two possible conclusions seem to be justifiable from the observations. First, a hypercoagulable state is induced as a direct result of the bleeding by a mechanism that is not clear. Second, a common factor might induce both the bleeding and the complication. It is possible, for instance, that a patient who is deteriorating might become sensitive to the anticoagulant and start bleeding. Since there were no differences in the composition of the groups, the latter hypothesis does not seem likely, and we are inclined to favor the first.

Whatever the mechanism, the results strongly point out that bleeding is a more undesirable complication than has generally been appreciated. To the risk of inducing a fatality as a direct result of bleeding there is added the more subtle risk of inducing a rebound complication that may be fatal. There are sufficient reports to indicate that the general incidence of a fatal bleeding episode during long-term anticoagulation is somewhere in the neighborhood of 1 per cent. The incidence of bleeding is around 10 per cent. If one assumes a bleeding rate of 10 per cent in patients on long-term treatment and a rebound (1 month) fatality rate of 16 per cent (seven out of 45 instances), then there could be expected to be 1.6 per cent greater mortality rate, making a total mortality rate of about 2.6 per cent. This is a figure comparable to that of many surgical operations and should instill further caution in the use of anticoagulants. Furthermore, reports that compare the future of patients who continue treatment with those who stop treatment because of bleeding are introducing a bias.
Summary

From a series of 310 patients on long-term anticoagulant treatment for various conditions 136 instances were collected in which treatment was interrupted. This was because of bleeding in 45 instances, for permanent reasons in 53 instances, and for temporary reasons in 38 instances.

Rebound thromboembolic complications were observed significantly more frequently in those who stopped treatment for bleeding. The cause of the rebound effect could not be ascribed to vitamin K1 administration, transfusions, or overt ischemic effects from blood loss although the latter might have been contributory to a small extent. The observations suggested a hypercoagulable state induced directly in some obscure way as a result of the bleeding.

 Interruption of treatment for reasons other than bleeding was not associated with early complications. The risk of interruption of treatment for short periods was relatively small (three nonfatal complications in 38 instances). In those who stopped permanently, complications were most often seen after 2 months.

Acknowledgment

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References

3. SISE, MOSCHOS, GAUTHIER, BECKER

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