The Rebound Phenomenon—Fact or Fancy?

Experience with Discontinuation of Long-Term Anticoagulation Therapy after Myocardial Infarction

By ROBERT VAN CLEVE, M.D.

There is considerable controversy regarding the recurrence of thromboembolic episodes following discontinuation of long-term anticoagulant therapy. Most reports from this country1-9 (table 1), claim a high incidence of thromboembolism after cessation of long-term anticoagulants. This is in striking contrast to what has been reported in some European studies.10-12 The question of a rebound state of hypercoagulability, especially after gastrointestinal bleeding necessitating stopping of anticoagulants, has been commented upon both in clinical and experimental studies.3, 5, 9, 13-16 Others have considered that the reported increase in thromboembolism is due to the natural history of the underlying disease when the "protection" from anticoagulants has been removed.17

The clinical studies supporting the concept of a rebound state of hypercoagulability following cessation of anticoagulant therapy have been mostly retrospective reviews. This paper reports the results of a prospective study in which long-term anticoagulant therapy for myocardial infarction was either abruptly stopped or gradually tapered. It is aimed at examining the existence of a clinical state of rebound hypercoagulability.

Description of the Study

A total of 134 patients with previous myocardial infarctions had been on coumadin therapy for an average of 3.6 years. They were seen at the San Diego Naval Hospital Outpatient Office. This group of retired officers, all male, represented an intelligent, stable group with similar backgrounds who followed instructions closely. It was decided to discontinue coumadin therapy in these patients.

These patients were divided into two groups. Group-I patients had coumadin stopped gradually over 6 weeks and group-II patients had anticoagulation abruptly terminated. Due to administrative policy random selection of these groups was not possible, but in general, those who saw the author during the first 6 weeks were in group I, and those after that in group II. None of the patients was lost to follow-up. In a third of the patients whose coumadin was discontinued abruptly, prothrombin times were checked subsequently once or twice weekly over a 2-week period. None remained above 16 seconds after this time.

In those patients tapered (group I), the dose was reduced at weekly intervals so that coumadin was stopped after the sixth week. The amount of reduction each week depended on the initial dosage, but was approximately 15 per cent of the original total dose. Prothrombin times were obtained on most patients at 1- or 2-week intervals. The interval before the prothrombin time reached 16 seconds or lower, varied from 1 to 5 weeks. The average time was 2.5 weeks. None remained elevated above 16 seconds after 6 weeks. These groups were followed for an average period of 12.2 months and 9.5 months. Group I comprised 63 patients; group II, 71.

Results

There were no episodes of embolism. There was only one case of thrombosis (myocardial infarction) among the 134 patients belonging to groups I and II during the first 6 weeks after discontinuing coumadin. This occurred in a group-II patient 2 days after coumadin was stopped and his prothrombin time at the time of myocardial infarction was 23 seconds with a control of 13 seconds.

There were nine thromboses (eight myo-
cardiac infarctions and one cerebrovascular accident) with five deaths in group I. In group II, there were seven thrombotic episodes (all myocardial infarctions) with four deaths. There were four autopsies in the group-I patients. Two of these revealed old and recent myocardial infarctions. In two other patients who died suddenly at home, there was evidence of old infarction. In group II, three autopsies were obtained. Two revealed old and new myocardial infarctions. The third revealed aortic stenosis with much focal myocardial scarring, but only slight coronary arteriosclerosis.

No autopsies were performed on two patients. One of these patients died suddenly at home, and one died suddenly in the hospital. These were presumed to be coronary deaths.

Coumadin was stopped in 14 patients after an episode of gastrointestinal, genitourinary, or other bleeding. Two of this group died (14 per cent). These were all placed in group II.

Discussion

This is the first reported study of a group of patients who were followed after long-term anticoagulation was stopped without specific indication (in 120 of 134). Most previous studies have been a tabulation of a retrospective collection of cases of those who have abandoned an anticoagulant program or in whom anticoagulants had to be stopped because of some contraindication to therapy. It is possible such selection may inject bias.

There was only one episode of thrombosis during the first 6 weeks after discontinuing coumadin in 134 patients. There was no notable difference among patients who had their coumadin stopped abruptly or gradually. These results suggest that there is no "rebound" hypercoagulability in respect to clinical thromboembolism following abrupt or gradual discontinuation of long-term coumadin therapy.

An increased risk of thrombosis after discontinuation of anticoagulation therapy following a bleeding episode has been noted by Sise et al. Of the 14 patients in this study in whom coumadin was stopped during a bleeding episode, two died. In contrast to Sise's study, no thrombotic episodes occurred during the first 6 weeks following cessation of therapy. One of these patients died suddenly during treatment of a recurrence of massive gastrointestinal bleeding. Several months previously he had had anticoagulation therapy stopped because of gastrointestinal bleeding.

Summary

Long-term anticoagulant therapy (coumadin) was gradually tapered over a 6-week period in 63 patients, and stopped abruptly in 71. All of these patients had been on coumadin following myocardial infarction. A

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Table 1

Review of Evidence for Enhanced Incidence Thromboembolic Events after Discontinuation of Long-term Anticoagulation*

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>Cosgriff</td>
<td>(embolic disease) 17 pts. stopped; 12 had 14 emboli; 8 within 4 weeks 6 within 3-23 months</td>
</tr>
<tr>
<td>1955</td>
<td>Alexander</td>
<td>considered theoretical possibility</td>
</tr>
<tr>
<td>1956</td>
<td>Keyes</td>
<td>28 pts. stopped (% due to bleeding); 14 MI's 3rd—20th month; 6 deaths</td>
</tr>
<tr>
<td>1958</td>
<td>Nichol</td>
<td>319 &quot;abandoned&quot; regimen; 20 died 1 mo; 18 mo. average follow-up 28% dead</td>
</tr>
<tr>
<td>1960</td>
<td>Dinon</td>
<td>66 stopped, highest recurrence 1st 6 weeks; 33% recurrence 1 yr.</td>
</tr>
<tr>
<td>1960</td>
<td>Thomas</td>
<td>13 (bleeding) stopped; 6 MI's 1 yr.; 4 deaths</td>
</tr>
<tr>
<td>1961</td>
<td>Kuhn</td>
<td>117 stopped; 5 deaths 1 month</td>
</tr>
<tr>
<td>1961</td>
<td>Sise</td>
<td>136 stopped; 53 recurrent; 7 fatal 1 year; 45 stopped after bleeding, 14 of 20 recurrence 4 weeks; 7 fatal 1 yr.; 16% mortality</td>
</tr>
<tr>
<td>1964</td>
<td>Van Cleve</td>
<td>Total 134 with previous MI's stopped; 1 recurrence 6 weeks; 16 thromboses after 11 mo. average follow-up with 9 deaths</td>
</tr>
</tbody>
</table>

*Note: None of the above series has had randomly selected controls.
careful follow-up showed that there was no difference in the incidence of thrombotic events in the first 6 weeks after discontinuation of therapy, whether this was stopped abruptly or gradually. These results suggest that clinically recognized "rebound" thrombosis does not occur after long-term coumadin therapy is stopped. There appears to be no hazard inherent in stopping long-term coumadin therapy abruptly. A possible exception to this is patients whose therapy must be stopped because of bleeding episodes.

References

Michael Servetus—1511-1553

“He who really understands what is involved in the breathing of man has already sensed the breath of God and thereby saved his soul.”—André Cournand, M.D. Circulation of the Blood. Edited by Alfred P. Fishman, M.D., and Dickinson W. Richards, M.D. New York, Oxford University Press, 1964, p. 23.
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