Prevention of Systemic Arterial Embolism in Chronic Rheumatic Heart Disease by Means of Protracted Anticoagulant Therapy

By John C. Wood, M.D., and Hadley L. Conn, Jr. M.D.

Seven clinic outpatients with mitral stenosis and auricular fibrillation complicated by systemic embolism have been maintained on Dicumarol for periods of 20 to 48 months. None has had a recognized embolism while on therapy. Dicumarol administration has been interrupted in each case for periods of six days to four months. Three additional systemic embolic episodes in two individuals occurred during this interval. Hemorrhagic manifestations have occurred on three occasions. The study suggests that: (a) protracted Dicumarol therapy is an effective means of preventing recurrent embolism in individuals with chronic rheumatic heart disease; (b) it is applicable to the average clinic outpatient.

SYSTEMIC arterial embolism is a recognized hazard in chronic rheumatic heart disease. Except for bacterial endocarditis which is not considered in this paper, it most commonly results from mural thrombosis complicating mitral stenosis with auricular fibrillation.

Following the successful employment of anticoagulants in the acute problems of thromboembolism, it was logical that their use should be extended to those individuals under chronic threat of embolism. The major question arising from this transition was whether anticoagulant drugs could be administered to the ambulatory patient without prohibitive risk of hemorrhage. This led Foley and Wright to select only “intelligent, co-operative private patients” in their exploratory work with outpatient treatment.1, 2 Since then a number of observations have been published, varying from casual references and isolated case reports to the extensive accumulated data of Cosgriff and Wright.3 to 12 The over-all experience suggests that prolonged anticoagulant therapy provides significant protection against recurrent embolism within the limits of an acceptable therapeutic risk.

This report presents our experience with the use of long-term Dicumarol* therapy as prophylaxis against recurrent systemic arterial embolism in patients with chronic rheumatic valvular disease who refused, or were rejected for, mitral valve surgery.

CASE MATERIAL

The series includes all individuals with rheumatic valvular disease followed in our Cardiac Clinic who have received Dicumarol over long periods of time to prevent recurrent arterial embolism (table 1). It consists of four females and three males with an age range at the time of initiation of therapy from 35 to 60 years. All have predominant mitral stenosis with chronic auricular fibrillation. Two patients (cases 2 and 6) have a minor degree of aortic valvular involvement. Cardiac classifications (American Heart Association) have ranged from II-B to IV-D. All patients have been placed on a restricted sodium intake and are receiving digitalis. Five have required mercurial diuretics. In each of the seven patients, anticoagulant therapy was instituted after one or more systemic embolic episodes.† Altogether 10 such episodes preceded treatment with Dicumarol (table 1).

The clinical diagnosis of arterial embolism involving an extremity (seven episodes) or the brain (one episode) was clearly warranted in each instance. Surgical confirmation was obtained in three patients at the time of embolectomy (cases 4 and 6) or ampu-

* 3,3′-methylenebis(4 hydroxycoumarin).
† Emboli to different sites occurring at the same time are considered as a single episode.

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TABLE 1.—Case Material

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Embolic Episodes Before Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>F</td>
<td>* RHD † M.S., A.I., A.F. ‡ II-B</td>
<td>(1) Abdomen (2) Right and left legs (3) Right femoral and left popliteal arteries</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>M</td>
<td>RHD M.S., A.I., A.F. III-C to II-B</td>
<td>(1) Aortic bifurcation Kidney</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>F</td>
<td>RHD M.S., A.F. II-B to III-C</td>
<td>(1) Brachial artery</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>RHD M.S., A.F. II-B to III-C</td>
<td>(1) Spleen (2) Right external iliac artery</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>F</td>
<td>RHD M.S., M.I., A.F. III-C</td>
<td>(1) Cerebrum</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>RHD M.S., M.I., A.S., A.F. II-C</td>
<td>(1) Left iliac artery Abdomen Flank</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>F</td>
<td>RHD M.S., A.F. IV-D to III-C</td>
<td>(1) Left popliteal artery</td>
</tr>
</tbody>
</table>

Total 7 patients

10 embolic episodes

* Chronic inactive rheumatic heart disease.
† M.S. = Mitral Stenosis; M.I. = Mitral Insufficiency; A.S. = Aortic Stenosis; A.I. = Aortic Insufficiency; A.F. = Auricular Fibrillation.
‡ American Heart Association Classification.
§ Emboli to different sites occurring at the same time are considered as a single episode.

tation (case 2). An otherwise unexplained episode of severe abdominal pain led to a presumptive diagnosis of visceral embolism in one individual (case 1). In one instance (case 4) left upper quadrant pain and tenderness accompanied by a transient friction rub indicated splenic embolism. Acute abdominal and flank pain accompanying sudden occlusion of the left iliac artery suggested associated visceral involvement in another instance (case 6). In one patient (case 2) renal embolism was thought likely because of a history of "mahogany" colored urine in conjunction with leg symptoms subsequently shown to be the result of a saddle embolus.

Method of Management and Results

Our method of administration and control of anticoagulants has been similar to the practice of others.1, 2, 6, 12 In six cases, therapy was begun immediately after an embolic episode; initially each received heparin until adequate prolongation of the prothrombin time was achieved with Dicumarol. In the seventh patient (case 5) Dicumarol was first given approximately one year after a cerebral embolism. All our patients were hospitalized during initial Dicumarol administration and stabilization. During the early outpatient period, prothrombin time determinations were done at four- to seven-day intervals. The time interval was subsequently increased to two weeks except for transient periods when hemorrhagic phenomena or erratic variations of the prothrombin times occurred. In one patient (case 5), a hospital employee under frequent clinical ob-
servation, intervals up to three weeks have been permitted.

Each individual has been thoroughly instructed in the potential danger of anticoagulants, and in the need for prompt action in the event of hemorrhagic manifestations. All have been encouraged to contact their clinic physicians by phone should any question as to therapy arise.

The average daily maintenance dose of Dicumarol has varied between 100 and 175 mg. in one patient, between 50 and 75 mg. in four, and between 25 and 50 mg. in the remaining two (table 2). At each clinic visit, a tentative Dicumarol dosage schedule has been arranged. This schedule has been confirmed, or altered if necessary, in a regular telephone report later the same day after the report of the prothrombin time was received.

This program has succeeded in maintaining prothrombin levels between 20 per cent and 35 per cent in most of the patients most of the time. In no case have we been able to avoid completely deviations above or below these limits. Variations of the prothrombin time beyond the desired range have been infrequent in four cases, occasional in two, and frequent in one. These results arbitrarily have been categorized as "good," "fair," and "poor control," respectively (table 2). Two patients (cases 2 and 3) are considered "good" by these criteria in spite of single episodes of bleeding.

Three individuals have had isolated instances of Dicumarol overdosage with hemorrhagic phenomena (table 2). These have consisted of microscopic hematuria and numerous leg petechiae in one (case 2); gross hematuria, skin ecchymoses and protracted bleeding following a minor laceration in a second (case 3); and gross hematuria, epistaxis, buccal ecchymoses and asymptomatic small retinal hemorrhages in the third (case 6). In two of the three instances, the patients had failed to keep their preceding clinic appointments. The intravenous administration of vitamin K₁ emulsion resulted in prompt cessation of bleeding and a return of the prothrombin time to safe levels within 24 hours in each instance. Blood transfusions were not required.

<table>
<thead>
<tr>
<th>Case</th>
<th>Average Daily Dicumarol Maintenance Dose (mg.)</th>
<th>Quality of Prothrombin Time Control</th>
<th>Hemorrhagic Episodes Complicating Dicumarol Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25-50</td>
<td>Good</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>50-75</td>
<td>Good</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>50-75</td>
<td>Good</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>25-50</td>
<td>Good</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>100-175</td>
<td>Fair</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>50-75</td>
<td>Poor</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>50-75</td>
<td>Fair</td>
<td>0‡</td>
</tr>
</tbody>
</table>

* Good—Infrequent deviations beyond 20–35% of normal prothrombin activity.
Fair—Occasional deviations beyond 20–35% of normal prothrombin activity.
Poor—Frequent deviations beyond 20–35% of normal prothrombin activity.

† Case 2. Microscopic hematuria and numerous leg petechiae.
Case 3. Gross hematuria, ecchymoses and prolonged bleeding following a minor laceration.
Case 6. Gross hematuria, epistaxis, buccal ecchymoses and asymptomatic small retinal hemorrhages.

‡ Case 7. Retroperitoneal hemorrhage in hospital when heparin was given after a lumbar sympathetic nerve block.

In addition, occasional small ecchymosis have occurred in two patients (cases 1 and 3) and slight gum bleeding associated with pyorrhea has been noted in another (case 4) when the prothrombin time was in the desired range.

While hospitalized, and prior to Dicumarol therapy, one patient (case 7) experienced retroperitoneal hemorrhage when heparin was given shortly after a paravertebral sympathetic nerve block. The incompatibility of lumbar sympathetic nerve block and anticoagulant administration has been stressed by others.¹³, ¹⁴

None of our patients has had a clinically apparent embolism while taking Dicumarol. Treatment has been given to individuals for periods varying from 20 to 48 months, or a combined total for all patients of 214 treatment months (table 3). Six patients are still being maintained on Dicumarol. In the seventh (case 7), Dicumarol was stopped after 15 months and a mitral commissurotomy was performed. At operation, no auricular
thrombus was found. Three days after surgery, anticoagulant therapy was resumed and continued for five months. It was then stopped because congestive failure had improved. This patient has not had an embolism since then, a period of seven months.

In all seven patients anticoagulant administration has been interrupted for periods varying from a few days to approximately four months, or a combined total for all patients of seven months (table 3). Except in one instance (case 4), this was done in anticipation of a dental extraction or a surgical procedure. Three additional embolic episodes in two individuals occurred during such an interval (table 3). One patient (case 3) had sudden occlusion of the right popliteal artery five days after Dicumarol was stopped and vitamin K₁ administered to permit cholecystectomy. One individual (case 4) was taken off Dicumarol by his family physician after an initial 17-month period of successful prophylaxis. Three months later he experienced left hemiparesis followed in one month by abrupt occlusion of the left popliteal artery concomitant with acute abdominal pain. At this time we placed him on a regular dose of Dicumarol once more. He has continued to take it to the present time, a period of 17 months, and has had no further embolism. A third patient was placed on heparin, as a preliminary to Dicumarol therapy, following a saddle embolus. Progressive ischemic necrosis of the left leg made necessary a supracondylar amputation. Heparin was withdrawn to permit surgery, shortly following which a probable pulmonary embolism occurred.

A total of 13 systemic embolic episodes, therefore, has occurred in the seven patients while not on Dicumarol during the combined pretreatment and withdrawal periods. In addition, one pulmonary embolism occurred when heparin administration was interrupted. In contrast, there has been no instance of embolism during the period of anticoagulant administration.

**Discussion**

The reported frequency of embolism in mitral stenosis with auricular fibrillation varies in different reports, possibly according to the duration of observation and manner of patient selection. Parkinson and Campbell and Viko and co-workers noted an incidence of 4 per cent and 8 per cent, respectively, without distinguishing between involvement of the pulmonary and systemic arterial sides of the circulation. However, it has been estimated that 20 per cent of these patients die from thromboembolism, the majority showing systemic embolic infarctions. Of patients selected by Janton and his associates for mitral
valve surgery, 22 per cent had experienced systemic arterial embolism. An incidence of 9 per cent was noted in another surgical series in which it was not specified whether all involved the systemic circulation. A recent clinicopathologic study revealed evidence of systemic arterial embolism, most of which had been manifest clinically, in 18 per cent of the cases. In a postmortem analysis of 164 cases of rheumatic heart disease where cardiac disability was severe and responsible for death, systemic and pulmonary infarcts were found in 45 per cent. It has been emphasized that visceral embolism found at autopsy had often been unsuspected clinically. Although an occasional individual may live for years following an embolism without a recurrence, repeated episodes are to be expected in the majority of patients, commonly following one another within six months.

The problem of prevention of recurrent embolism in this condition has not been completely solved. The main preventive therapeutic procedures which have been tried clinically include conversion to sinus rhythm with quinidine, prolonged anticoagulant regimens, left auricular appendage ligation or resection, and mitral commissurotomy.

A difference of opinion exists as to the danger of embolism associated with conversion of auricular fibrillation to normal sinus rhythm with quinidine. However, it is generally felt that the risk of quinidine administration is increased and the maintenance of sinus rhythm difficult in the presence of rheumatic heart disease and long-standing auricular fibrillation, especially when accompanied by congestive heart failure. Therefore, the use of quinidine in this situation has not gained wide acceptance. Today, in the presence of mitral stenosis, surgery limited to resecting the left auricular appendage seems ill-advised. It has been demonstrated that mural thrombi in chronic rheumatic heart disease are situated in regions other than left auricular appendage in more than 50 per cent of the cases. Secondly, left auricular appendectomy or ligation would complicate, if not prevent, a subsequent attempt to open the mitral valve.

Mitral commissurotomy is probably the method of choice in handling this problem at the present time, although embolism in the operative or immediate postoperative period is a hazard. There will remain some patients who are not suitable for, or who refuse, surgery and a group with recurrence after mitral valvulotomy. In these individuals long-term anticoagulant therapy seems indicated. The complete freedom from embolism in our patients during a total treatment period of over 200 patient months is in sharp contrast to the pretreatment period and to the occurrence of three additional systemic emboli during the total period of seven patient months when Dicumarol was withdrawn. Our experience, combined with previous observations, has led us to have the following point of view concerning the use of long-term Dicumarol therapy in patients with rheumatic mitral valvular disease:

1. Absolute protection against embolism is not necessarily to be expected. Insurance against dislodgement of preformed mural thrombi cannot be provided. It is difficult, if not impossible, to maintain a therapeutically effective prothrombin time in all patients at all times.

2. Because of the close individual attention required for safe anticoagulant administration and the fact that many patients with mitral stenosis and auricular fibrillation do not experience clinically apparent embolism, we have limited Dicumarol therapy to those persons with preceding embolic manifestations. Possibly a subgroup of these patients who (a) are in the older age range, (b) have a severe degree of mitral stenosis, and (c) have congestive failure might be selected as suitable for long-term treatment. Further study of this problem seems indicated.

3. Because of the danger of local hemorrhage, it is probably good judgment to avoid using anticoagulants immediately following a cerebral embolism.

4. Dicumarol should not be administered to ambulatory patients in the absence of adequate laboratory and clinical control. The latter demands alertness of the physician as well as cooperation on the part of the patient. Careful education of the patient concerning
the purpose and toxicity of Dicumarol is important. It makes practicable, for the average clinic outpatient, an anticoagulant program where the period between laboratory checks is fixed on what must be conceded to be an arbitrary basis. Unpredictable variations in the effect of Dicumarol are not entirely eliminated by weekly prothrombin time determinations.

(5) Provided the requirements of (4) are met, serious hemorrhage rarely should occur although occasional hemorrhagic manifestations are to be anticipated. These generally can be controlled readily with vitamin K₁ which is superior to water soluble analogs.27, 28

(6) Once instituted, unless the basic situation is altered, as by mitral commissurotomy, there is no way of selecting a point of safe withdrawal. Therefore, therapy probably should be continued indefinitely in most patients. Although not substantiated, the possibility exists that a temporary state of relative hypercoagulability may follow withdrawal of anticoagulants.

(7) Recognizing the foregoing limitations, protracted Dicumarol therapy appears to be a reasonably effective means of preventing recurrent embolism.

In the use of Dicumarol on an outpatient basis, we have been inclined to err in the direction of inadequate prolongation of the prothrombin time to reduce the risk of hemorrhage. Some reassurance in this policy is gained through our own favorable results and the empiric observations of others that protection appears to be afforded with less prothrombin suppression than the generally accepted range of 10 or 15 per cent to 30 per cent.1, 2, 6, 12

Summary

Seven clinic outpatients with mitral stenosis and chronic auricular fibrillation complicated by previous systemic arterial embolism have been maintained on anticoagulant therapy for periods of 20 to 48 months. No patient has had a recognized embolism while on therapy. Two individuals had further systemic embolism during periods of temporary Dicumarol withdrawal. An additional patient experienced pulmonary infarction when heparin administra-

tion was interrupted. Hemorrhagic phenomena of a degree sufficient to necessitate therapy with vitamin K₁ have occurred on three occasions.

This study suggests that long-term Dicumarol administration is an effective means of preventing recurrent embolism in individuals with chronic rheumatic heart disease and that it is applicable to the average clinic outpatient.

Addendum

Since the writing of this paper, one patient (case 4) has had an episode of mental confusion and apparent slight right-sided weakness which cleared without residuum within 24 hours. This occurred when the prothrombin value was 32 per cent. It is felt reasonable to consider this as an embolic episode.

Sumario Español

Siete pacientes ambulatorios con estenosis mitral y fibrilación auricular crónica complicada con previos émbolos arteriales sistémicos han sido mantenidos en terapia anticoagulante por períodos de 20 a 48 meses. Ningún paciente ha tenido un embolismo reconocido durante la terapia. Dos individuos tuvieron embolismos reconocidos durante períodos de descontinuación temporal del Dicumarol. Un paciente adicional experimentó un infarto pulmonar cuando la administración de heparina se interrumpió. Fenómenos hemorrágicos de suficiente grado para requerir tratamiento con vitamina K₁ ocurrieron en tres ocasiones.

Este estudio sugiere que la administración por largo término de Dicumarol es un medio efectivo para la prevención del embolismo recurrente en individuos con enfermedad reumática cardíaca crónica y que es aplicable al paciente promedio ambulatorio.

References

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