Anticoagulant Therapy in Private Practice

By CHARLES A. L. STEPHENS, JR., M.D.

One hundred eighty-one patients suffering from 216 separate episodes of thromboembolism were treated with anticoagulants by the author in private practice. The indications and contraindications for anticoagulants are described and the results tabulated and analyzed. Practical methods of administration of anticoagulants are discussed. Long-term ambulatory anticoagulant therapy is considered as a special and important aspect of the problem of thromboembolism with the results indicating it to be a practical and feasible form of preventive therapy worthy of more widespread use.

THE DISCOVERY of heparin by McClean in 1916 and the identification ofbishydroxycoumarin (Dicumarol) by Link and his co-workers in 1934 as the agent responsible for sweet clover disease in cattle, stimulated studies of the clinical use of anticoagulant therapy. The excellent work of Jorpes, Zilliacus, Barker of the Mayo Clinic, and Wright of New York, and others has crystallized the indications and contraindications and evaluated the benefits and dangers of this form of therapy in thromboembolic disease.

There remain some, however, who question the value of anticoagulant therapy. There are others who maintain that these drugs can be safely and effectively administered only by a few experts supported by a Research Laboratory or a teaching hospital.

During the past six years in private practice in the community of Tucson, Arizona, the author has successfully administered anticoagulant therapy to 181 patients suffering from thromboembolic conditions. It is the purpose of this report to review this experience and to demonstrate that anticoagulant therapy is a practical, feasible and effective form of therapy in private practice in a small community.

METHODS

It was felt that anticoagulant therapy was indicated in any patient who suffered from thromboembolism and in whom one or more of the contraindications listed below did not exist. Heparin and/or Dicumarol was given to patients suffering from those diseases listed in table 1.

Anticoagulant therapy was not administered to patients suffering from one or more of the diseases listed in table 2. Anticoagulant therapy was administered with caution under the conditions listed in table 3.

Selection of the Anticoagulant. Heparin was chosen whenever an immediate anticoagulant effect was desired. Patients with pulmonary embolism or those with thrombophlebitis where pulmonary emboli might be anticipated are examples of need for immediate anticoagulant effect. Heparin was not given to patients suffering from coronary thrombosis with myocardial infarction because: (1) evidence indicates that the first 36 hours after infarction are not attended by a high thromboembolic morbidity or mortality; (2) heparin therapy is of necessity disturbing to a patient who might profit more by rest and supportive measures during the first few days. Dicumarol was chosen as a maintenance anticoagulant in all cases capable of taking oral medication.

Method of Administration. When given, heparin was administered intravenously every four hours. The initial dose was 50 mg. Three hours later a Lee-White coagulation test was performed and on the fourth hour the heparin was again administered intravenously with the exceptions noted below. This was continued around the clock. If the Lee-White coagulation time was below 20 minutes, 75 mg. were given. If it was between 20 and 30 minutes, 50 mg. were given, and if it was between 30 and 45 minutes, 25 mg. were given. If it was above 45 minutes no heparin was administered on the fourth hour.

The difference in patient response was not determined by the heparin tolerance test. Heparin in Pitkins menstruum or Depo-Heparin with or without a vasoconstrictor was not used. The evidence of Barker and his co-workers indicates that absorption of these preparations is too variable to insure either an effective or safe therapeutic level. There are no well controlled studies reported to date indicating the value or safety of intramuscular heparin in a retarding menstruum.

The thermostability of heparin and the variable patient tolerances necessitates the continued use of the Lee-White test. It has been found that different batches of heparin vary in their effect on the same patient, possibly because of exposure to high temperatures in transit. This may be an important factor in warm climates.

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TABLE 1.—Indications for the Use of Anticoagulants

1. Heart disease with auricular fibrillation and mural thrombi.
2. Coronary occlusion and myocardial infarction.
3. Cerebral thromboses.
4. Peripheral arterial thromboses.
5. Mesenteric thromboses.
6. Arterial embolism.
7. Thrombophlebitis and/or "phlebothrombosis."
8. Pulmonary embolism.
9. Central retinal artery or vein thrombosis.

It has been helpful to both patient and technician to insert a child's spinal needle or a polyethylene tube in a vein in the forearm to facilitate the administration of heparin and the withdrawal of blood for coagulation tests.

Dicumarol was given by mouth. The initial dose was 300 mg. and 24 hours later, 200 mg. were administered. Lesser amounts were used in patients in whom caution was felt to be necessary. (See table 3.)

The prothrombin time was determined daily by means of the Link-Shapiro modification of the Quick method and the value desired was two to two and one half times the control. Experience has confirmed the necessity of drawing blood for the prothrombin time just prior to the next dose of heparin, for heparin will influence the prothrombin time. Heparin was discontinued when the prothrombin time reached an adequate therapeutic level and the patient was then maintained on Dicumarol.

Continuation of Therapy. Anticoagulant therapy was continued as long as the patient exhibited active thromboembolic disease. In instances where the etiology or evidence of the thromboembolic disease persisted, the patient was maintained on anticoagulant therapy in an ambulatory fashion. In no instances was the heparin or Dicumarol discontinued abruptly, but the drug was tapered off over a period of 7 to 10 days.

TABLE 2.—Contraindications for the Use of Anticoagulants

1. Duodenal or gastric ulcer.
2. Gastric carcinoma.
4. Severe hypertensive disease.
5. Cirrhosis of the liver.
6. Hepatitis.
7. Dissecting aneurysm of the aorta.
8. Preceding a traumatic operation, such as transurethral resection.
11. Late pregnancy.

TABLE 3.—Conditions Requiring Caution in the Use of Anticoagulants

1. Hypoprothrombinemia.
2. Acute or chronic passive congestion of the liver (heart failure).
3. Thrombotic thrombocytopenic purpura.
4. Impending delivery or non-traumatic surgery.
5. Renal insufficiency.

In those patients in whom anticoagulant therapy was continued on an ambulatory basis, prothrombin determinations were made once weekly, (rarely once in two weeks), for it was felt that the patient was under better control if the prothrombin time was determined once every seven days. The result of the prothrombin time was recorded on a specially designed form, and the dosages for the following seven days were recorded on this same sheet. The patient was then informed by telephone what his dosage of Dicumarol should be for the coming week.

This method of ambulatory anticoagulant therapy requires very little time or effort on the part either of patient or doctor and has permitted patients on such therapy to lead full and active lives without interference or fatal thromboembolism.

RESULTS

Anticoagulant therapy has been administered for the past six years to 181 patients suffering from thromboembolic disease. Prior to treatment there were 216 thromboembolic episodes in these 181 patients. There were five additional patients who were given anti-

TABLE 4.—Nature of Thromboembolic Episodes Occurring in 181 Patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophlebitis</td>
<td>88</td>
</tr>
<tr>
<td>Coronary thrombosis</td>
<td>55</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>16</td>
</tr>
<tr>
<td>Auricular fibrillation with intra-auricular</td>
<td>12</td>
</tr>
<tr>
<td>thrombosis</td>
<td></td>
</tr>
<tr>
<td>Cerebral thrombosis</td>
<td>11</td>
</tr>
<tr>
<td>Peripheral arterial occlusion</td>
<td>10</td>
</tr>
<tr>
<td>Peripheral emboli</td>
<td>9</td>
</tr>
<tr>
<td>Buerger's disease</td>
<td>6</td>
</tr>
<tr>
<td>Central retinal vein thrombosis</td>
<td>3</td>
</tr>
<tr>
<td>Mesenteric thrombosis</td>
<td>2</td>
</tr>
<tr>
<td>Phlebitis migrans</td>
<td>1</td>
</tr>
<tr>
<td>Polyecythemia</td>
<td>1</td>
</tr>
<tr>
<td>Multiple sclerosis (experimental)</td>
<td>2</td>
</tr>
<tr>
<td>Prevent thrombosis</td>
<td>5</td>
</tr>
</tbody>
</table>

|                                   | 221             |
Hemorrhage

There were 105 males and 76 females. The age of the patients varied from 16 years to 88 years.

The distribution of the pretherapy thromboembolic episodes is shown in table 4. Heparin was administered as an initial anticoagulant to 96 cases (53 per cent) and all received Dicumarol therapy. (See table 4.)

Hemorrhage

Of the 181 patients given anticoagulant therapy major bleeding occurred in 12 patients (7 per cent). (See table 5.) Minor bleeding occurred in 36 patients (20 per cent). (See table 6.)

Two deaths could possibly be attributed to Dicumarol therapy. The first occurred in a 72 year old white woman who suffered from cerebral arteriosclerosis and multiple cerebral thrombi and who died of a cerebral hemorrhage. The second death occurred in a 69 year old white man who suffered from a coronary thrombosis with posterior myocardial infarction and while on adequate anticoagulant treatment suffered another myocardial infarction one week later. At postmortem examination hemorrhage into the wall of the anterior descending coronary artery was found. Such phenomena are, however, frequently encountered in patients not on anticoagulants.

The maximum over-all mortality from hemorrhage due to anticoagulants might therefore be considered to be 0.11 per cent. All bleeding occurred in patients receiving Dicumarol; there were no episodes of hemorrhage while on heparin.

Therapy of Hemorrhage. Cessation of anticoagulant therapy constituted the major form of treatment of bleeding due to anticoagulants. In four instances vitamin K (recently K₁ oxide) was given and in only one case was whole blood transfusion a necessary addition. Because no bleeding occurred as a result of heparin therapy protamin was not used.

Thromboembolism

There were two episodes of new thromboembolism while on anticoagulant therapy (0.11 per cent). The first of these was in a woman with auricular fibrillation and probable mural thrombus with a previous history of multiple peripheral emboli who had one embolus to the right leg eight days after anticoagulant treatment was started. No further emboli have occurred in this patient.

Table 5.—Major Hemorrhage

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Gross hematuria</td>
<td>7</td>
</tr>
<tr>
<td>(b) Gross melena</td>
<td>2 (due to diverticulae)</td>
</tr>
<tr>
<td>(c) Hematemesis</td>
<td>1 (due to gastric cancer)</td>
</tr>
<tr>
<td>(d) Cerebral hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>(e) Hemorrhage in wall of coronary</td>
<td>1</td>
</tr>
</tbody>
</table>

12 (7 per cent)

Table 7.—Mortality While on Anticoagulants

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6</td>
</tr>
<tr>
<td>Collagen disease</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
</tr>
</tbody>
</table>

* All were examined post mortem and there was no further thromboembolism present.

Table 6.—Minor Bleeding

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Microscopic hematuria</td>
<td>12</td>
</tr>
<tr>
<td>(b) Petechiae and ecchymoses</td>
<td>7</td>
</tr>
<tr>
<td>(c) Bleeding gums</td>
<td>6</td>
</tr>
<tr>
<td>(d) Soft tissue hematomata</td>
<td>7</td>
</tr>
<tr>
<td>(e) Epistaxis</td>
<td>4</td>
</tr>
</tbody>
</table>

36 (20%)
after five and one-half years of continuous therapy on an ambulatory basis.

The second was an elderly white man with polycythemia rubra and multiple episodes of venous thrombosis; four days after starting treatment with heparin and Dicumarol and two days after discontinuing heparin therapy acute thrombophlebitis developed in a lower extremity. The prothrombin time at the time of onset was 39 seconds with a control of 15 seconds. Continuation of treatment with Dicumarol led to subsidence of the thrombotic episode.

Ambulatory Anticoagulant Therapy

Fifty-three patients were continued on long term anticoagulant therapy for a total of 15,507 days of therapy. This averages 293 days per patient. The range was from 38 days to 2,045 days. Of this group 10 died of causes unassociated with thromboembolic phenomena while on therapy. (see Table 7.)

The remaining cases (43 patients) continued anticoagulant therapy for variable periods of time. Therapy was eventually discontinued in 15 of the cases for the reasons listed in table 8, and two of this group continued anticoagulant therapy at home under the care of their local physicians. Twenty-six of this group are currently still on ambulatory anticoagulant therapy without untoward episodes of either bleeding or thromboembolism.

Of the seven patients who stopped anticoagulant therapy against advice, five died thereafter of thromboembolism; two remain alive and well two and four years respectively, after discontinuing treatment. (See table 8.)

Comments

No statistically valid conclusions can be drawn from the data in this study other than the observation that anticoagulant therapy can be safely and effectively administered in private practice. The incidence of thromboembolism while on therapy of 0.11 per cent and the incidence of major hemorrhage (7 percent) are not in excess of and, in most instances, are below the complications reported in other studies.9

The effectiveness of the procedure can only

be implied from the numbers of cases here reported. Short-term therapy has been well substantiated by larger controlled studies by others.19, 20 Ideally, long-term ambulatory anticoagulant therapy should be evaluated by similar controlled and statistically valid studies. This presents great practical difficulties. However, it should be pointed out that out of seven of our patients who discontinued therapy against advice, five are dead of thromboembolism in contrast to an incidence of fatal thromboembolism in those who continued therapy of 0 per cent.

The experience of the author confirms that of others that ambulatory anticoagulant therapy properly applied is a life-preserving measure.

Conclusions

1. Acute and chronic thromboembolic conditions can be successfully treated with anticoagulants in private practice with a reasonable conscientious effort on the part of the patient and his physician.

2. This can be carried out satisfactorily in private practice in a small community provided that: (a) there are laboratory facilities capable of producing accurate thrombin determinations; (b) the physician will assume the responsibility inherent in this form of therapy.

3. The incidence of complications in this series agreed favorably with those reported from teaching hospitals and research laboratories.

4. The results of this and other studies warrant more extensive investigation and use of ambulatory anticoagulant therapy.

Sumario Español

Ciento ochento y uno pacientes sufriendo con 216 episodios diferentes de tromboembolismo fueron tratados con anticoagulantes por el autor en su práctica privada. Las indicaciones y contraindicaciones para el uso de anticoagulantes se describen y los resultados se tabulan y se analizan. Métodos prácticos para la administración de los anticoagulantes se discuten. La terapia ambulatoria con anticoagulantes a término prolongado se considera como un aspecto especial e importante en el
problema del tromboembolismo con resultados que indican ser una forma práctica y factible de terapia preventiva meritoria de uso más extenso.

REFERENCES

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