THE EFFECT OF 3,3′-METHYLENE-*BIS*-(4-HYDROXYCOUMARIN) (DICUMAROL) ON THE PROTHROMBIN AND COAGULATION TIMES OF BLOOD

THREE YEAR SUMMARY

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In July 1942 the results of the use of dicumarol in 23 patients were reported.[1] Since that time the drug has been administered to 70 additional patients, making a total of 93. After the article of Butt, Allen, and Bollman[2] on the administration of dicumarol in man numerous articles appeared. These were summarized by Gefter, Kramer, and Reinhold[3] in 1944 in a comprehensive review of the literature and a report of 30 cases of thromboembolic disease in which the preparation was used.

Clinical conditions for which dicumarol was administered. The table classifies conditions for which dicumarol was administered at the Cleveland Clinic up to March 1945. The largest group consisted of acute superficial thrombophlebitis. These cases were differentiated from those of deep thrombophlebitis because the degree of clinical response seemed to vary. The second largest group consisted of cases of retinal thrombosis involving the vein or artery. The remaining cases were of postoperative pulmonary embolus, thromboangiitis obliterans, coronary thrombosis with infarction of the myocardium, and peripheral arterial thrombosis, either secondary to heart disease or caused by arteriosclerosis obliterans (table).

TABLE

Diagnosis	No. of Cases
Acute superficial thrombophlebitis	28
Deep thrombophlebitis	10
Thromboangiitis obliterans	8
Coronary thrombosis	7*
Arteriosclerosis obliterans with thrombosis	7
Subacute bacterial endocarditis	6
Thrombosis of retinal vein	20
Thrombosis of retinal artery	3
Postoperative pulmonary embolism	4
TOTAL	93

* Three treated at another hospital.

Method of administration. The administration of dicumarol presents an interesting but difficult problem. Various methods have been proposed. Meyer, Bingham, and Pohle[4] recommended an initial dose of 5 mg. per kilogram body weight followed by $\frac{1}{6}$ to 1 mg. per kilogram daily. Among others Gefter, Kramer, and Reinhold[3] used this method in their series of 30 cases. My clinical experience, however, showed that this method of administration was difficult to control, inasmuch as the effect of dicumarol is cumulative, and maximum changes in the prothrombin time usually do not occur until forty-eight hours after administration. In this series the only toxic effects including hematuria followed the continuous daily administration of dicumarol. Although the method as described appears to be ideal, I found the complications attendant to its use excessive.

I have not been able to work out accurately any method of administration based on body weight. Moreover, in the oral administration of any preparation allowance must be made for the numerous variable factors that frequently make any measurable constant result impossible to estimate. This seems to be especially true of the oral administration of dicumarol.

It did seem possible, however, to administer this drug by certain methods whereby an average result could be anticipated: Adults weighing under 150 pounds received 250 mg. orally the first day and 100 mg. on the second and third days. Those weighing over 150 pounds received 300 mg. orally the first day and 150 mg. on the second and third days. The drug was then discontinued. The prothrombin time was estimated before administering dicumarol and every other day thereafter. An attempt was made to elevate the prothrombin time to 30 to 45 seconds. Levels below 30 seconds were relatively ineffective, and although levels above 45 seconds rarely produced hematuria, the results were not commensurate with the increase.

Usually the prothrombin time rose promptly between twenty-four and forty-eight hours, the peak being reached from the fifth to the eighth day, and returned to normal from the tenth to the twelfth day. If the patient responded to the drug according to this pattern and if no toxic signs appeared, a follow-up dose of 100 to 150 mg. was given, depending upon the body weight, provided that further elevation of the prothrombin time was desired. This small dose usually resulted in an elevation lasting from five to six days, whereupon the dose was repeated if necessary. Since a corresponding rise in the coagulation time does not always occur, the more consistent effect upon the prothrombin time determine its use as an index. In these studies the Lee and White method for estimating the prothrombin time was used.

COMMENT

It has been definitely demonstrated that dicumarol increases the prothrombin time in man. The effect, however, is not always constant in persons of similar ages and weights suffering from the same disease. Because of possible deviations and the need for both clinical and laboratory observations, dicumarol is not a satisfactory preparation to be used in general office practice. All patients receiving the drug should be hospitalized and the indications for its administration carefully studied.

Indications and contraindications. The use of dicumarol should be considered in any condition showing acute arterial or venous thrombosis. The use of dicumarol is contraindicated in subacute bacterial endocarditis. Two of six patients treated with dicumarol in conjunction with other methods of therapy died in the hospital. In one, death was found to be due to cerebral hemorrhage, and in the other, to a pulmonary embolus. In neither patient did the prothrombin time exceed 35 seconds. It is fair to assume that cerebral hemorrhage as the cause of death in the first patient was related to the increased prothrombin time. In the second patient the increased prothrombin time did not prevent the pulmonary accident. In general, patients suffering from subacute bacterial endocarditis have fluctuations in prothrombin time with a tendency toward abnormal bleeding, and therefore the drug should not be used in treatment.

Dicumarol is also contraindicated in the presence of any chronic liver or renal disease, especially when there is a deficiency of vitamin K or demonstrable decrease in urinary function. Blood dyscrasias with bleeding tendencies and any existing prothrombin deficiency, such as may occur with jaundice or nutritional disease, are contraindications. The drug should not be used in any open ulceration because local hemorrhage may readily occur.

Toxicity. The commonest toxic effect of dicumarol is hematuria. This occurred in five patients. In two, whole blood given intravenously promptly checked the bleeding. In three cases in which no therapy was given the hematuria cleared up spontaneously. I have not used vitamin K intravenously in large doses to lower the prothrombin time. Cromer and Barker[6] reported beneficial results from its use in treating excessive hypoprothrombinemia induced by dicumarol. The only other hemorrhagic manifestation was the one case of subacute bacterial endocarditis terminating with cerebral hemorrhage. At postmortem examination no evidence of liver damage was observed.

No unusual effects were noted on the hemoglobin, erythrocyte count, leukocyte count, or urine. In the series reported by Gefter[3] no unusual effects were noted in other laboratory investigations.

Results. In this series dicumarol was used chiefly in cases of superficial acute thrombophlebitis, and when used in the early stages, during the first two weeks, the course of the disease seemed to be moderately checked. In deep thrombophlebitis or phlebothrombosis dicumarol did not seem to produce any beneficial clinical effects. In thrombosis of the retinal veins improvement in vision was noted in 50 per cent of the patients. In the remaining 50 per cent none of the eyes were enucleated owing to secondary glaucoma. In coronary thrombosis and thrombosis of the peripheral arterial circulation recovery was satisfactory, although it is not possible to ascertain the course of the disease in these patients if dicumarol had not been used. Results were compared with those of other methods of treatment in patients with similar clinical and laboratory findings.

In a group of patients suffering from postoperative pulmonary embolism no deaths occurred. In April 1943 a large series of cases was reported by the Mayo Clinic in which dicumarol was given routinely to patients having abdominal hysterectomies, and the incidence of pulmonary embolism was greatly reduced.[5] It has been noted that patients with an increased clot retraction time have a higher incidence of postoperative pulmonary embolism than those showing a normal clot retraction time. In this group, therefore, the prophylactic use of dicumarol might be advisable.

My experience with dicumarol in the treatment of thromboangiitis obliterans has been limited but does not indicate that this drug is an effective part of treatment.

Advantages. The cost of dicumarol is exceptionally low, and it tends to have an effective and prolonged action when given orally, which makes intravenous therapy unnecessary. In these respects it is probably more advantageous to use than heparin. On the other hand, dicumarol is not effective for twenty-four to forty-eight hours, and if immediate action is desired, heparin should be given intravenously. When combined treatment is indicated, heparin is administered intravenously at the outset, and dicumarol given orally at the same time. When dicumarol becomes effective at the end of the first or second day, heparin may be discontinued. It may be noted here that heparin has a more constant effect on the coagulation time than it does on the prothrombin time, whereas the opposite is true of dicumarol.

SUMMARY

In 93 cases of thromboembolic disease the effects of dicumarol as a part of treatment were observed from clinical and laboratory standpoints. Dicumarol is effective in increasing the prothrombin time of the blood; however, this effect is not constant, and no specific or routine method of administration can be proposed at present. The drug should be used cautiously, and the patient to whom it is administered should be hospitalized for careful observation.

The dicumarol was supplied by Eli Lilly and Co., Indianapolis, Ind.

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