The Effect of [3,3′—Methylene—Bis—(4-Hydroxycoumarin)] (Dicumarol) on the Prothrombin and Coagulation Times of the Blood

Preliminary Report

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After experimenting with spoiled sweet clover for several years, Link and his associates[1] in 1941 isolated the active hemorrhagic factor (3,3′—methylene—bis—(4-hydroxycoumarin)] and were able to produce it by synthesis. This work was probably stimulated by the observations of Schofield[2] and Roderick.[3] Although it had been known for many years that cattle occasionally showed signs of hemorrhage for no obvious reason, it remained for these workers to demonstrate that this hemorrhagic tendency was related to the eating of spoiled sweet clover. In June 1941 Butt, Allen, and Bollman[4] reported that the oral administration of this compound to animals and man prolonged the prothrombin and coagulation times with an effect similar to that of heparin.

During the past six months this drug has been used clinically in over 20 cases in which such a reaction would be helpful in the management of the patient. Table 1 shows the clinical conditions treated.

Disease	No. of Cases
Pulmonary embolism postoperative	4
Acute thrombophlebitis	8
Rheumatic heart disease with subacute bacterial endocarditis	6
Thrombo-angiitis obliterans	4
Thrombosis retinal vein	1
Total cases	23

The following three cases are presented to show the effects of [3,3′—methylene—bis (4-hydroxycoumarin)] on the prothrombin and coagulation times.*

Although no name has been definitely adopted for this preparation, it will be referred to as dicumarol in the following cases. These are among the earlier cases treated with this drug, and as yet the dosage has not been standardized. As will be observed, the drug was used in varying

*The Quick method is used for coagulation time, and Lee and White method for prothrombin time.

amounts without regard to body weight. However, the reactions have been helpful in determining a more reliable form of dosage which at the present time is calculated chiefly on body weight.

Case 1. A man, aged 29, was admitted to the Clinic April 17, 1942 complaining that pain, weakness, chills and fever had been present for two months. Physical examination revealed that this patient was suffering from rheumatic heart disease, mitral stenosis, and insufficiency. Blood culture at the time of admission was positive for streptococcus viridans. A final diagnosis of subacute bacterial endocarditis was made.

My experience with various forms of treatment for this condition has been unsatisfactory, although the usual forms of chemotherapy have been applied for some time.

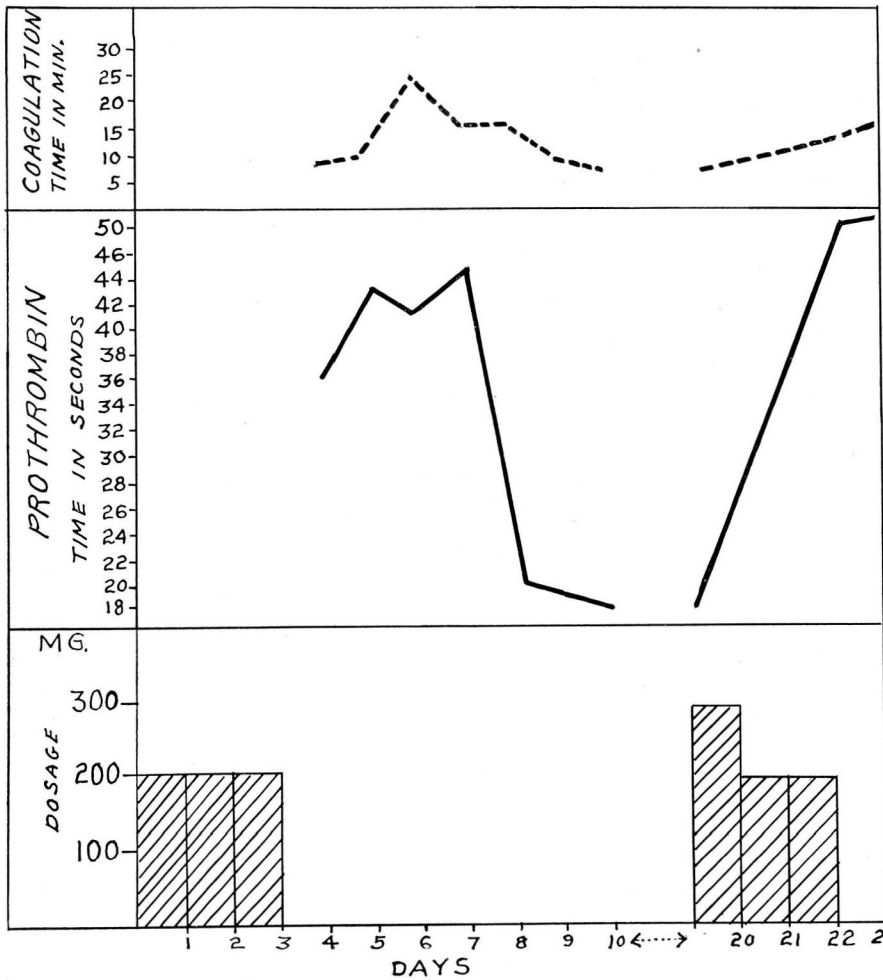

CHART 1

Heparin also has been used in combination with some of the sulfonamide preparations. Because much of the effect of dicumarol is similar to that of heparin, it seemed logical to apply this preparation along with some of the sulfonamide drugs. For this patient sulfadiazine was combined with dicumarol. The patient was hospitalized, and on the first three days of hospitalization he was given 200 mg. of dicumarol daily. Chart 1 indicates the effect of this drug on the prothrombin and coagulation times. At the end of the third day there was a definite rise in the prothrombin time, the normal being 15 seconds. Medication was withdrawn on the third day, and at the end of the tenth day the prothrombin time had returned to normal. The coagulation time reached a peak of 25 minutes corresponding to the peak of the prothrombin time. The patient was dis-

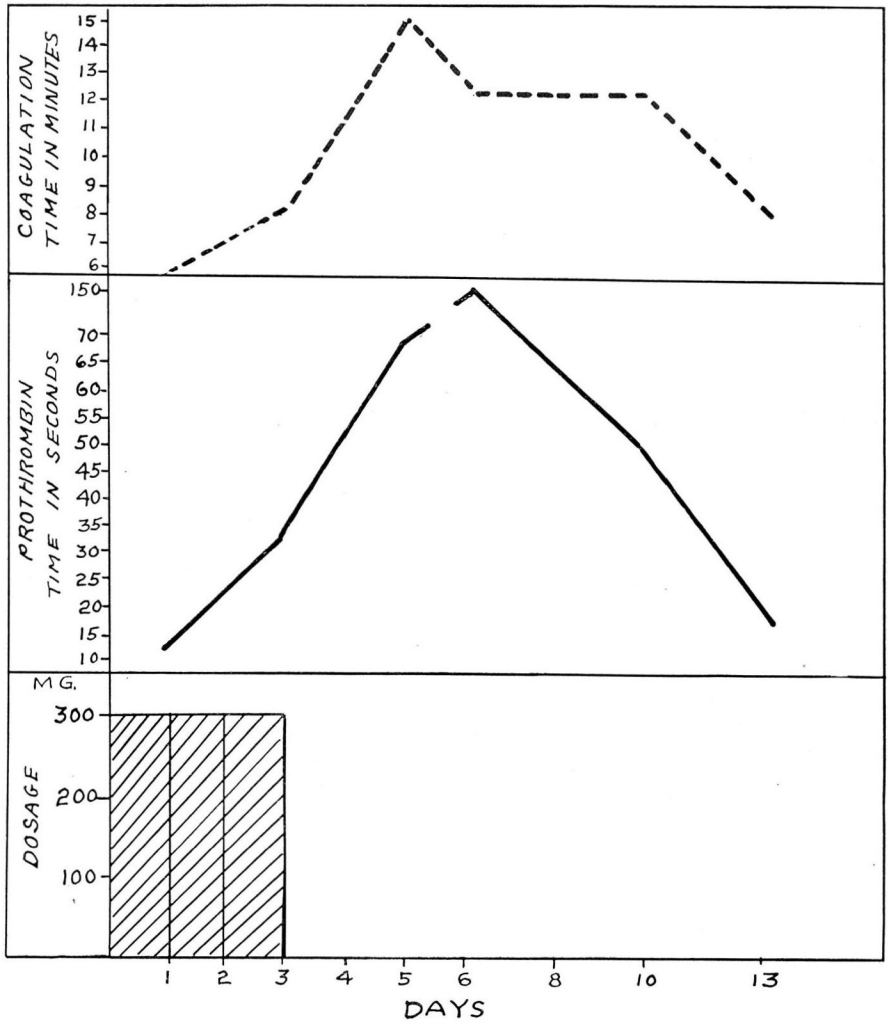

CHART 2

charged from the hospital on sulfadiazine therapy which he continued at home. When he was readmitted to the hospital ten days later, the prothrombin and coagulation times were normal, and he was given a second dose as indicated on the chart. There was an immediate response which again lasted for ten days. This patient was followed for a period of several months following the initial use of the drug. The dosage was repeated on several occasions at intervals of about 14 days, and the reaction seemed to be fairly constant in each instance.

Although adequate levels of sulfadiazine were maintained, the patient continued to become steadily worse and died two months after starting treatment. During the course of treatment it seemed that the number of embolic reactions was reduced, although he continued to have them from time to time.

Case 2. A woman, aged 32, weighing 100 pounds was admitted to the Clinic May 5, 1942. Her complaints were referrable entirely to the extremities. Examination indicated marked reduction in the peripheral circulation, and ulceration in several areas of the toes and fingers. After careful vascular studies a diagnosis of thromboangiitis obliterans was made. It is the first case in a woman that I have observed. The patient was hospitalized and various forms of treatment started in an attempt to improve the peripheral circulation. Because of the nature of the disease it was felt that any agent which might increase the prothrombin and coagulation times might be of help in the management of this type of patient.

Chart 2 indicates the patient's response. A total of 900 mg. of dicumarol was given given over a period of three days. On the seventh day the prothrombin level rose to 150 seconds. At the same time there was a slight drop in the coagulation time to 12 minutes, the highest peak being 15 minutes. At no time during the course of treatment was there any evidence of hemorrhage. As far as could be determined, she suffered no ill effects from a rather marked change in the prothrombin time. The coagulation and prothrombin times returned to normal in approximately 13 days. Inasmuch as other forms of treatment were employed at the same time, it was impossible to tell whether or not this patient received any benefit from this type of preparation.

Case 3. A man, aged 42, weighing 175 pounds was admitted to the Cleveland Clinic Hospital April 8, 1942 with an extensive acute thrombophlebitis. The etiology was not determined. There was no involvement of the peripheral arterial system. Previously, heparin has been used in this type of case, and, accordingly, dicumarol seemed to be the ideal drug. Chart 3 represents the patient's reaction. He was given 200 mg. of dicumarol on the first day and 100 mg. on the second and third days. A prompt response was noted in both the prothrombin and coagulation times, and at the end of ten days, there was still some elevation. The patient made a rather rapid clinical recovery and has been observed regularly since his discharge from the hospital. Again it was impossible to determine the effects of this drug on the course of the disease as the patient was in bed. Frequently, the symptoms respond promptly to bed-rest alone.

COMMENT

The chief purpose of this report has been to show the effect of dicumarol on the prothrombin and coagulation times. Although several clinical conditions have been treated with this drug, it is impossible to state at the present time whether or not any benefit has been derived from its use. Observations would indicate that the drug is effective in

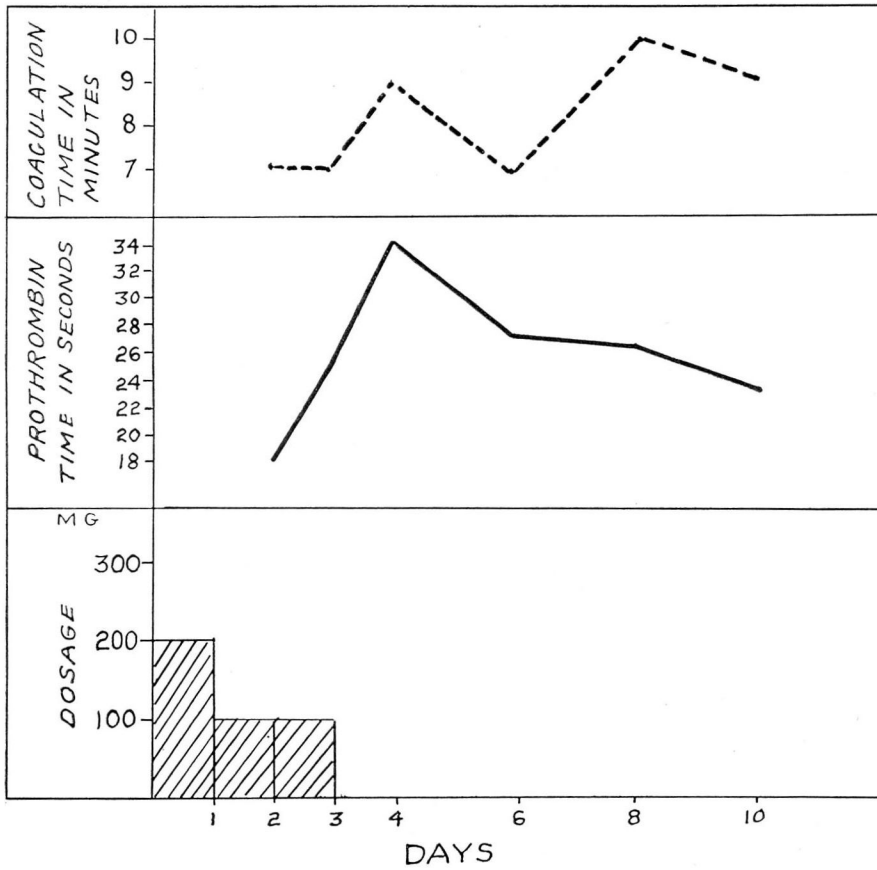

CHART 3

increasing the prothrombin and coagulation times. As a general rule, there is a delay in the rise of about 24 to 48 hours. At the end of this time with proper dosage there should be a prompt rise in both levels which is maintained for 10 to 12 days. The drug may be administered again at the end of this time with a prompt rise in the levels. Although no standard dosage has been worked out, an initial oral dose of 5 mg. per kilo. seems to be effective. A subsequent equal dose on the two following days can be given with safety and produces an adequate rise in both the prothrombin and coagulation times. Recently, I have been inclined to reduce the dose on the third day to 2½ mg. per kilo.

Because of the rather marked fluctuations that are obtained by the present method of administering the drug, an attempt has been made to

establish a small daily maintenance dose. This seems to be the ideal way to administer the drug, and no doubt in the near future the proper dosage by weight will be determined. Dicumarol also has been given intravenously, but I have had no personal experience with this method of administration.

It does not seem necessary to raise the prothrombin levels as high as in the cases presented in this report, although no untoward effects have been observed during this study. The effect of dicumarol on the hemoglobin level, red blood cell count, and white blood cell count was observed, and at no time were any abnormalities found. Lower levels of prothrombin and coagulation times are desirable until further experience and more confidence in the safety of the drug has been established. There is no direct relationship between the rise in prothrombin and coagulation times.

SUMMARY

A small series of cases has been treated with dicumarol, and the reactions are reported. Dicumarol has a definite effect upon the prothrombin and coagulation times. As yet its therapeutic value has not been established.

We are indebted to Dr. F. B. Peck of Eli Lilley and Co. for furnishing us with the material and indication to dosage.

BIBLIOGRAPHY

1. Campbell, H. A., Smith, W. K., Roberts, W. L., and Link, K. P.: Studies of the hemorrhagic sweet clover disease. I. The preparation of hemorrhagic concentrates, J. Biol. Chem. 136: 47-55, October, 1940.
2. Schofield, F. W.: Damaged sweet clover: the cause of a new disease in cattle simulating hemorrhagic septicemia and blackleg, J. Am. Vet. M.A. 64:553-572, February, 1924.
3. Roderick, L. M.: The pathology of sweet clover disease in cattle. J. Am. Vet. M.A. 74:314-325, February, 1929.
4. Butt, H. R. et al: A preparation from spoiled sweet clover [3,3′—methylene—bis—(4—hydroxycoumarin)] which prolongs coagulation and prothrombin time of the blood, Proc. Staff Meet. Mayo Clinic, 16:388-395, June 18, 1941.