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Treatment of Dicoumarol-Induced Hypoprothrombinemic Hemorrhage with Vitamin K_1 Oxide.*

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Retardation of the rate of coagulation of human blood may be accomplished by the use of heparin or of dicoumarol (3-3′-methylenebis [4-hydroxycoumarin]). The action of heparin may be neutralized by protamine;[1] that of dicoumarol by vitamin K_1 oxide.[2] Under the influence of dicoumarol, spontaneous hemorrhages have been reported in cattle,[3] dogs,[4] and man.[5] In man the possibility of spontaneous hemorrhage following the administration of dicoumarol must not be overlooked, especially since in any given individual the tendency to bleed, and the time of appearance and intensity of the induced hypoprothrombinemia cannot be predicted. In our experience, a single large oral dose of dicoumarol (0.8 to 1.0 g) will produce an appreciable drop in the prothrombin concentration within 24 hours. The period of induction of satisfactory therapeutic hypoprothrombinemia may take 5 or more days, and the period of spontaneous recovery following discontinuance of the drug from 6 to 10 or more days.

Oral doses of dicoumarin varying between 150 and 300 mg fail to produce satisfactory changes in the plasma prothrombin concentration and coagulation time of the whole blood as tested by our methods.[6] Davidson and MacDonald[7] showed that the coagulation time of the blood, when tested in lusteroid tubes, was significantly prolonged before any alteration was demonstrable by the usual glass tube methods. The whole blood coagulation time, when tested in glass tubes (Lee and White method), does not appear to be significantly altered until the prothrombin concentration is depressed to 5% of normal. Therefore, in order to obtain a suitable prolongation of the whole blood coagulation time in the shortest possible period, we have used larger doses of dicoumarol (0.6 to 1.0 g daily) than those recommended in the literature.[8]

The hypoprothrombinemia induced by vitamin K deficiency is usually corrected by the administration of vitamin K compounds[9] that induced by dicoumarol appears to be refractory to the usual dosage of vitamin K and is only partially rectified by the transfusion of whole blood.[10,8,7] Davidson and MacDonald[2] reported that in human subjects, a very large dose of vitamin K_1 oxide will correct the hypoprothrombinemia produced by a single large dose of dicoumarol.

This report deals with the control of hemorrhage and the correction (by the administration of a single large dose of vitamin K_1 oxide) of the hypoprothrombinemia induced by repeated large doses of dicoumarol.

Case. No. U 99827. E.P., a white male, age 22 years, complained of lumbar pain associated with low grade fever and followed by a propagative right-sided femoral thrombophlebitis. Chart 1 shows the effects of treatment with heparin and dicoumarol.† Early in the

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1 Chargaff, E., *J. Biol. Chem.*, 1938, **125**, 671.

2 Davidson, C. S., and MacDonald, H., *New Engl. J. Med.*, 1943, **229**, 353.

3 Campbell, H. A., Roberts, W. L., Smith, W. K., and Link, K. P., *J. Biol. Chem.*, 1940, **136**, 47.

4 Stahmann, M. A., Huebner, C. F., and Link, K. P., *J. Biol. Chem.*, 1941, **138**, 513.

5 Cahan, A., *New Engl. J. Med.*, 1943, **228**, 820.

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7 Davidson, C. S., and MacDonald, H., *Am. J. Med. Sci.*, 1943, **205**, 24.

8 Meyer, O. O., Bingham, J. B., and Axelrod, V. H., *Am. J. Med. Sci.*, 1942, **204**, 11.

9 Aggeler, P. M., and Lucia, S. P., *Acta Med. Scand.*, 1941, **107**, 179.

10 Bingham, J. B., Meyer, O. O., and Pohle, F. J., *Am. J. Med. Sci.*, 1941, **202**, 563.

† Supplied by E. R. Squibb and Company.

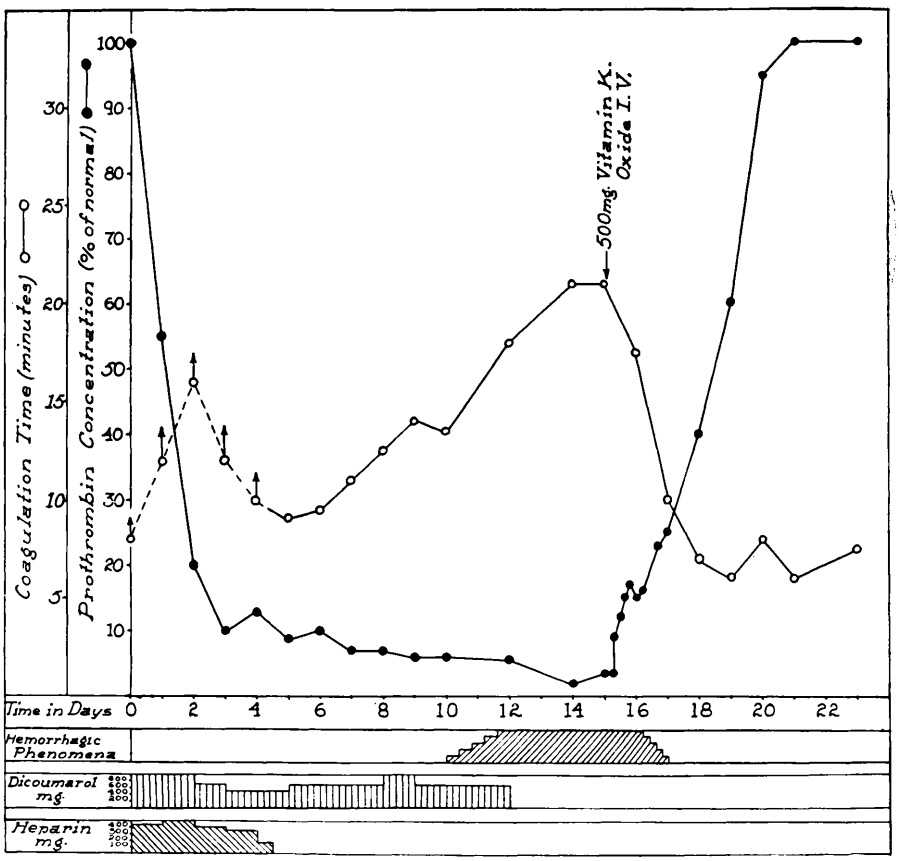

CHART I.

course of the illness, the whole blood coagulation time was retarded by intermittent intravenous doses of heparin,‡ while the effects of dicoumarol were being induced by the daily administration of 500 to 1000 mg oral doses of the drug.§ The prothrombin concentration dropped readily and was maintained at low levels for several days before significant alterations in the whole blood coagulation time occurred. Hematuria developed on the tenth day of dicoumarol medication and continued until the seventeenth day. During this time the patient had frequent epistaxis, ecchymoses at the site of hypodermic injections and bleeding from herpetic lesions on the lips. Dicoumarol treatment was discontinued on the twelfth day and on the fifteenth day 500 mg of vitamin K_1 oxide were given intravenously according to the method described by Davidson and MacDonald.[7] After a latent period of 4 hours, there was a dramatic elevation of the prothrombin level, although recovery from the hemorrhagic manifestations was delayed 24 hours. Full correction of the hypoprothrombinemia was achieved within 5 days. The thrombophlebitic process rapidly regressed after treatment with heparin and dicoumarol.

Summary. In a human subject, hypoprothrombinemia and the secondary hemorrhagic phenomena induced by multiple large doses of dicoumarol appeared to be corrected by the intravenous administration of a single massive dose of vitamin K_1 oxide. The period of time elapsing between the institution of treatment with vitamin K_1 oxide and the cessation of hemorrhagic phenomena is too long to make this method entirely satisfactory.

‡ 185 cc of Connaught Laboratories heparin was administered in 4½ days.

§ Total dosage of dicoumarol 9750 mg taken over a period of 12 days.