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BLOOD ANTICOAGULANT COMPOSITION

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1 Claim. (Cl. 167—65)

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This invention relates to new compositions which are particularly adapted to reduce or prevent clotting of the blood, and more particularly refers to compositions of dicoumarol and a compound which induces clotting of the blood.

It is known that dicoumarol is a most effective anticoagulant. Unfortunately its use has been seriously curtailed because it is so powerful in its action that there is an ever present danger of hemorrhaging on the part of the patient. If a slight excess of dicoumarol is administered, hemorrhaging is likely to occur. Thus, the use of this material, despite its valuable anticoagulant property, is subject to serious consequences in the event of a slight overdose. The problem is further complicated by the fact that a dosage of dicoumarol which might be satisfactory on one day would be too much the following day. This is due to the fact that the body synthesizes vitamin K and this counteracts the effect of the dicoumarol. Synthesis of vitamin K by the body, however, varies from day to day, and may vary from a few micrograms per day up to as much as two or three milligrams. With such an extreme variation in the amount of vitamin K produced by the body, it is readily apparent that to determine the optimum dosage of dicoumarol is almost an impossible task. Hence the refusal of many doctors to employ this unusually effective anticoagulant.

It is an object of this invention to produce compositions containing dicoumarol which, while preserving its exceptional anticoagulant properties, at the same time minimize the danger of an overdose, thereby permitting its widespread use without meticulous controls. Additional objects will become apparent from a consideration of the following description and claim.

In accordance with our invention, we have found that the effectiveness of dicoumarol is dependent to a large extent upon the ratio between the dicoumarol and the vitamin K present in the body. Where the amount of vitamin K is extremely small the ratio between the two is of course very large and a slight variation in the amount of vitamin K produced in the body results in a substantial change in this ratio. By means of our invention we prepare compositions of dicoumarol containing substantial amounts of vitamin K or one of the known substitutes for this material, such as menadione. The dicoumarol is present in these compositions in an amount greater than that needed to overcome the effect of the vitamin K and produces a net anticoagulant effect. Because of the presence

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of substantial amounts of vitamin K it is at once evident that the ratio in the body between the dicoumarol and the vitamin K will be but slightly changed by any variation in the amount of vitamin K which is naturally synthesized. As a result, our compositions, for all practical purposes, minimize the extreme effects heretofore resulting from the natural synthesis of vitamin K during administration of dicourmarol.

In view of the expense attendant upon the use of vitamin K, it is advisable to use one of the cheaper substitutes which are known to possess the same blood coagulating properties. Menadione, which is 2-methyl-1,4-naphthoquinone, as well as other vitamin K substitutes or mixtures thereof, may be used for this purpose.

We prefer to use in our compositions approximately 100 parts by weight of dicoumarol and approximately 8 parts by weight of menadione. If naturally occurring vitamin K were used in place of menadione, the amount thereof would be decreased to compensate for its greater coagulant effectiveness. It is to be understood that the foregoing ratio may be varied widely without departing from the scope of this invention.

As an example of the composition which is effective in treating or preventing clotting of the blood, we may mix 100 milligrams of dicoumarol and 8 milligrams of menadione. Where a greater anticoagulant effect is desired, the amount of dicoumarol may be increased accordingly, and the converse is likewise true.

As a preferred embodiment of our invention, we may likewise incorporate in the compositions referred to previously vitamin P to produce a strengthening of the capillary walls, thereby reducing the possibility of rupture. For this purpose vitamin P may be used in the form of hesperidin, hesperidin methyl chalcone, and phosphorylated hesperidin. The advantage of employing this material is that it further minimizes the possibility of hemorrhaging, since it strengthens the structure of the blood vessels, and as long as these vessels are prevented from rupturing there can be no hemorrhage.

A composition employing vitamin P is as follows:

	Milligrams
Dicoumarol	100
Menadione	8
Hesperidin methyl chalcone	10–20

By means of our invention the prothrombin level of the blood for each patient may be deter-

mined in accordance with customary procedure, and a composition of dicoumarol and vitamin K prepared to produce an anticoagulant effect in that patient. Due to the large vitamin K content of this composition there is practically no likelihood that the patient will hemorrhage as the result of subsequent variations in the amount of vitamin K synthesized in the patient's body.

Our compositions are particularly adapted for use in the prophylaxis and treatment of intravascular clotting, in postoperative, post-traumatic and postinfectious thrombophlebitis, pulmonary embolism, acute embolic or thrombotic occlusion of peripheral arteries, recurrent idiopathic thrombophlebitis, and the like.

As many apparently widely different embodiments of this invention may be made without departing from the spirit and scope hereof, it is to be understood that the invention is not limited to the specific embodiments hereof except as defined in the appended claim.

We claim:

An anticoagulant composition comprising approximately 100 parts of dicoumarol, approximately 8 parts of 2-methyl-1,4-naphthoquinone and approximately from 10 to 20 parts of a member of the class consisting of hesperidin, hesperidin methyl chalcone and phosphorylated hesperidin.

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