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Effect of Rutin on Dicoumarolism.*

WILLIAM G. CLARK.

From the Scripps Metabolic Clinic, La Jolla, Calif.

As far as the writer is aware, no drug has been described which exerts a specific antagonistic action on the hemorrhagic symptoms of dicoumarolism.

Dicoumarol has been shown to increase bleeding time and this is not correlated with increased prothrombin time.[1,2] Capillary fragility, moreover, is not altered in patients with hemorrhagic symptoms after excessive dicoumarol.[2,3] Dicoumarolism also causes marked dilation of capillaries, small arteries and veins.[4,5] Other toxic vascular changes include marked swelling and vacuolization of endothelium, with areas of endothelium proliferation, degeneration of vascular smooth muscle, perivascular serous exudation and diapedesis of blood cell elements and even necrosis and rupture of the entire vessel wall.

Flavonoid derivatives ("vitamin P"-like substances) have been shown to decrease bleeding time,[6,7] capillary permeability and fragility. Rutin is a well-known flavonoid described as having anti-capillary fragility action by Sevin,[8] later by Griffith, Couch and Lindauer[9] and since then by many others. Widespread clinical application of rutin has resulted, with conflicting reports. An extensive literature exists[10] on the purported anti-hemorrhagic properties of flavonoids and related substances in diverse pathologic states, both experimental and clinical. The mechanism of such action, if true, is not clear, but may be related to either reduction in the size of the capillary bed,[11] or to an antihyaluronidase action.[12-15]

Prandoni and Wright[2,3] noted no effect of "vitamin P" in the form of grated orange peels orally administered to patients suffering hemorrhagic symptons from dicoumarol therapy. The quantity of flavonoids administered by this method is small and the nature of the flavonoids contained in orange peel is largely unknown other than hesperidin and eriodictyol.

Naghski, Copley and Couch[16] reported that the flavonol glycosides, rutin and quercitrin, and quercetin (aglucone of rutin) exert an antagonistic effect against the bacteriostatic effect of dicoumarol and therefore suggested the possibility of using rutin or similar flavonols to antagonize the hemorrhagic action of dicoumarol *in vivo*.

The present note presents evidence which indicates that rutin has no protective action against dicoumarolism in rats.

Experimental. Male albino rats (Slonaker

* Supported by a grant from the United States Public Health Service.

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strain) were divided into 2 groups of 10 each, averaging 137 g body weight and 2 months of age. Both groups were fed Purina Laboratory Chow mash in which was incorporated 0.04% dicoumarol.† One group received this diet alone and the other received the same diet containing 2% rutin‡ in addition to the dicoumarol. From the average daily food intake it was estimated that each rat ingested about 0.3 mg dicoumarol daily, and the rutin-fed animals ingested about 150 mg rutin daily. Later, as the animals became poisoned, less food was consumed. Records were kept of the hemorrhagic symptoms, body weight loss and survival.

The experiment was terminated after 30 days, at which time there were no survivors in the group fed dicoumarol alone, with an average survival time of 15 days (range 7 to 19); and 10% surviving in the group fed rutin + dicoumarol, with an average survival time of 13 days (range 5 to 21), of the rats which died.

In a second experiment of 10 rats per group, average body weight 120 g, the dietary dicoumarol was adjusted to 0.02% instead of 0.04% as in the first experiment, and the rutin, as before, remained at 2%. The experiment was terminated after 45 days, at which time 90% of the controls survived (the one death occurred in 45 days), and 60% of the rutin-fed animals survived (the 4 deaths occurred in 7, 22, 41 and 44 days).

In a third experiment of 10 rats each, average body weight 140 g, the animals were fed Purina Chow and the dicoumarol ± rutin were stomach-tubed daily as aqueous suspensions in doses of 5 mg dicoumarol ± 50 mg rutin. After a week, the dose of dicoumarol was increased to 10 mg, since 5 mg seemed insufficient to evoke hemorrhagic symptoms. The experiment was terminated in 35 days, at which time 30% of the controls were surviving, with an average survival time of 26 days for the rats which died; and 20% of the rutin-fed animals were surviving, with an average survival time of 18 days for the rats which died.

There were no group differences in onset or severity of hemorrhagic symptoms in the 3 experiments.

Conclusions. Under the experimental conditions employed, rutin does not antagonize dicoumarolism in rats. Presumably the defect in the vessel walls or their supporting structures which leads to hemorrhage in dicoumarolism differs from that leading to the various hemorrhagic conditions which rutin and related "vitamin P"-like substances purportedly benefit. These facts, however, need not necessarily preclude the simultaneous use of dicoumarol and "vitamin P" for their separate effects, as illustrated by the report of MacLean and Brabel[17] on the favorable effects of rutin and dicoumarol in various retinal vascular disorders.

† Kindly supplied by E. R. Squibb & Sons, New York.

‡ Kindly supplied by the S. B. Penick Co., New York.

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