11542

Absorption of Water-Soluble Vitamin K from Intestinal Tract.*†

E. D. WARNER AND JOSEPH E. FLYNN.

From the Department of Pathology, State University of Iowa, Iowa City, Iowa.

Bile salts are known to be essential for the absorption of fat-soluble forms of vitamin K from the intestinal tract, but it is not known whether they are of benefit in the absorption of the water-soluble forms. To obtain data regarding this, we have used bile-obstructed rats in which the vitamin K reserves were depleted preoperatively by the technic previously reported from this laboratory.[1] After ligation of the bile duct, the animals were placed on a diet[2] from which vitamin K was still more rigidly excluded. Within 3-4 days the prothrombin level falls into the bleeding zone. The subsequent rise in prothrombin, following the oral administration of vitamin K, was used as a measure of the extent to which the vitamin is utilized, either with or without supplements of bile salts.

Prothrombin determinations were made by the 2-stage technic of Warner, Brinkhous, and Smith;[3,4] bile salts (1 cc of 3% sodium taurocholate) and vitamin K were given through a metal tube into the stomach. As a source of water-soluble vitamin K, we used the potassium salt of the disulfuric acid ester of 2-methyl-1,4-naphthohydroquinone. Since this work was initiated the sodium salt of this compound was described by Fieser.[5] It is apparently somewhat less potent[6] than 2-methyl-1,4-naphthoquinone, when the two

* Aided by a grant from the John and Mary R. Markle Foundation. Funds for assistance were also supplied by the Graduate College, State University of Iowa.

† The potassium salt of the disulfuric acid ester of 2-methyl-1,4-naphthohydroquinone, used in these experiments, was prepared in November, 1939, as a part of a cooperative program in which a series of compounds of this type was synthesized by George H. Coleman, J. J. Carnes and D. W. Kaiser of the Department of Chemistry, State University of Iowa.

1 Flynn, Joseph E., and Warner, E. D., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 190.

2 Tidrick, Robert T., Joyce, Frank T., and Smith, H. P., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 853.

3 Warner, E. D., Brinkhous, K. M., and Smith, H. P., *Am. J. Physiol.*, 1936, **114**, 667.

4 Smith, H. P., Warner, E. D., and Brinkhous, K. M., *J. Exp. Med.*, 1937, **66**, 801.

5 Fieser, L. F., and Fry, E. M., *J. Am. Chem. Soc.*, 1940, **62**, 228.

6 Ansbacher, S., Fernholz, E., and Dolliver, M. A., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 652.

TABLE I.
Response of Rats* to a Water-soluble Form of Vitamin K.

Days of treatment	Prothrombin levels (% of normal) 2 γ of vitamin daily	5 γ of vitamin daily	8 γ of vitamin daily
	Results with vitamin K plus bile salts.		
0	24	19	17
1	14	52	57
2	dead†	52	78
			106
	Results with vitamin K but without bile salts.		
0	15	12	29
1	14	16	50
2	15	38	86
3		55	—
4		68	91

* Albino rats weighing 200 to 300 g.
† Autopsy showed extensive intraäbdominal hemorrhage.

compounds are compared on a molar basis. Our own experience indicates that the compound is non-toxic when given orally to rats in doses 100 times the physiological requirements.

Results. Table I shows typical examples of the response of K-deficient rats following administration of daily doses of 2, 5 and 8 μg of the water-soluble compound. It is readily seen that bile salt did not appreciably modify the therapeutic efficacy of the vitamin. At the level of 2 μg, the prothrombin level remained in the bleeding zone. At the level of 5 μg, the recovery was 35-70% complete, both with and without bile salt, and with daily doses of 8 μg the prothrombin rose above the 75% level.

When fat-soluble forms of vitamin K are administered to man, the danger always exists that the dose of bile salt will not be adequate in amount, or that the bile salt may not mingle properly with the vitamin following dissolution of the capsules. The oral administration of water-soluble vitamin K, if effective in man, will eliminate this problem. It will also eliminate much of the nausea and vomiting produced by the bile supplements. It is obvious that when the acute phase of the disease subsides, bile salt should then be given to enable absorption of the many fat-soluble components of the diet.