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Effect of Vitamin K on Clotting Factors in Children with Congenital Cyanotic Heart Disease

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The effect of intramuscularly and orally given vitamin K_1 on prothrombin-complex activity (Quick-value) and on the activity of factors II, V and VII has been investigated in 15 children with congenital cyanotic heart disease. Oral administration proved ineffective, whereas parenterally given vitamin K caused significant increases in prothrombin-complex activity and in the level of factors II and VII, in the majority of cases. It has been concluded that the haemorrhagic disorders found in some of the children with congenital cyanotic heart disease, may be ascribed to a reduced absorption of vitamin K and/or to impaired liver function.

The tendency to bleeding of patients with congenital cyanotic heart disease, associated with hypoxaemia and secondary polyglobulia has been well established. The bleeding tendency has been attributed to various factors such as thrombocytopenia [14], a reduced blood level of clotting factors [4] or the increased fibrinolytic activity of blood [5].

A lower level of clotting factors may result either from decreased production or increased consumption. The question whether the haemorrhagic disturbance of these patients is a consumption coagulation defect, has been a matter of dispute [3, 5]. Our previous studies have answered this question partly in the positive. Although intravascular clotting decreases the platelet count, extensive studies have revealed that a low activity of clotting factors may be associated with normal platelet counts which is incompatible with the consumption theory. The assumption of a disturbance in clotting factor synthesis seems therefore plausible. This may result either from (i) vitamin K deficiency, caused *a)* by the insufficient production of this vitamin by the intestinal flora, or *b)* by a disturbance in its absorption, or, else, (ii) from liver damage. The present study has been designed to determine the relative importance of the above factors.

MATERIAL

Fifteen children, aged 3 to 14 years, were involved in the experiments. They all had cyanotic congenital heart disease,

a normal platelet count (over 150.000 per cu.mm) and subnormal or nearly normal values for prothrombin-complex activity (Quick-value) and for factor II, V and VII. Routine laboratory findings did not suggest any impairment of liver function; serum protein level and composition, serum bilirubin, thymol turbidity and SGOT activity were within the normal range. The haematocrit was between 64 and 81%. During the period of observation the patients were given no drugs interfering with blood clotting (antibiotics, sulphonamides, etc.). No signs suggestive of haemorrhage or thrombosis could be detected.

Ten children aged from 4 to 10 years with congenital non-cyanotic heart disease served as controls. They received no drug therapy, and their laboratory findings indicated normal haematologic conditions and liver function.

Method

(i) The effect of intramuscularly given vitamin K was assessed after the administration of 5—8 mg of vitamin K_1 daily for two days, in both groups.

(ii) The effect of orally administered vitamin K was studied after the children had been given 5—8 mg of vitamin K_1 daily for three days.

Periods of oral and muscular administration of vitamin K_1 were separated by a minimum interval of fourteen days. In order to avoid dilution of the plasma by the 3.8% sodium citrate used to prevent clotting of blood samples, a correction to the actual haematocrit was performed.

The following parameters were determined before and after vitamin K administration: haematocrit, by microassay; prothrombin-complex activity (Quick-value) by the single stage technique of Quick, as modified by Schultze [8], using thrombokinase (Geigy) as reagent; activity of factors II, V and VII, using Behring preparations [8]. Activities were expressed in percent of the normal.

Student's *t* test was used for statistical analysis of the data.

Table I

Changes in Quick-value and in the activity of factors II, V, and VII on intramuscular and oral administration of vitamin K_1

I: Initial value, II: value after the administration of 5—8 mg vitamin K_1. ns.: Non-significant

Group	Route of administration	No. of cases	Quick value		factor II		factor V		factor VII	
			average %	*p*	average %	*p*	average %	*p*	average %	*p*
Control, intramuscular	I	10	93	> 0.05 n.s.	98	> 0.05 n.s.	90	> 0.05 n.s.	89	> 0.05 n.s.
	II		95		98		91		95	
Cyanotic, intramuscular	I	15	59	< 0.01	50	< 0.01	59	> 0.05 n.s.	50	< 0.01
	II		73		74		60		72	
Cyanotic, oral	I	15	52	> 0.05 n.s.	50	> 0.05 n.s.	63	> 0.05 n.s.	54	> 0.05 n.s.
	II		53		53		63		56	

Results

The stable haematocrit level during the period of observation indicated that the changes observed were not due to a concentration or dilution of the blood.

The results obtained are summarized in Table I.

In the non-cyanotic controls the activity of clotting factors was within the normal range. Intramuscular administration of vitamin K caused no significant changes in these parammeters.

In the group with cyanotic heart disease the activity of factor II (prothrombin) and factor VII (proconvertin) and the Quick-value increased significantly ($P < 0.01$, see Fig. 1). The initial level of factor V (proaccelerin) was generally higher, being

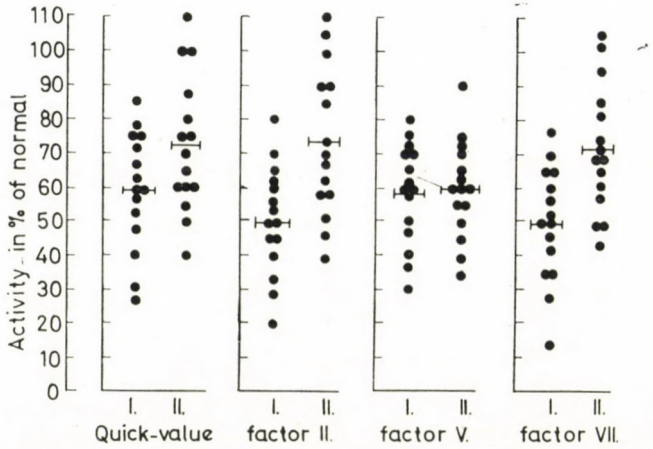

Fig. 1. Effect of intramuscular vitamin K_1 in patients with cyanotic heart disease. I: initial value; II: value after vitamin K treatment

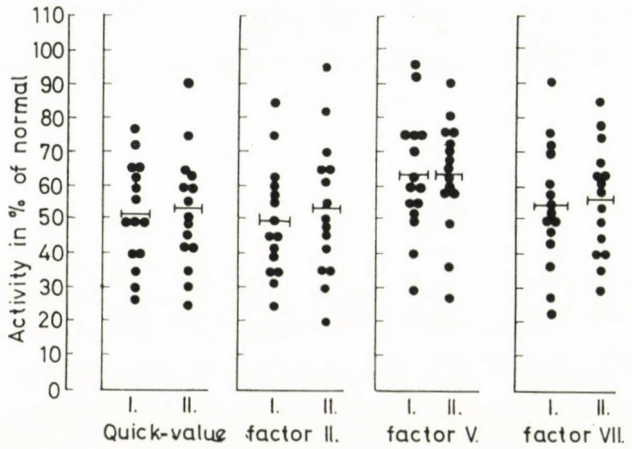

Fig. 2. Effect of oral vitamin K_1 in patients with cyanotic heart disease. I: initial value; II: value after vitamin K treatment

above the lower normal limit of and its changes on intramuscular vitamin K were insignificant ($P > 0.05$).

Oral administration of vitamin K to the cyanotic children caused insignificant increases in the levels of the factors examined ($P > 0.05$, see Fig. 2).

Discussion

Most of the clotting factors are produced by the liver (fibrinogen, factors II, V, VI, VII, VIII, IX, X and XII). The synthesis of some factors (II, VII, IX and X) proceeds only in the presence of vitamin K [9, 11].

In man, vitamin K is produced in sufficient amounts by the intestinal flora, covering the entire need of the organism. Absorption of vitamin K depends on normal bile secretion. As to the role of the absorbed vitamin in the synthesis of clotting factors, there are only hypothetic considerations, such as

1. Vitamin K would constitute a part of the molecule of some of the clotting factors [2].

2. Vitamin K plays an important role in oxidative phosphorylation, while the rate of formation of clotting factors highly depends on the activity of this process [10, 12].

3. Vitamin K would influence the genetic control of the synthesis of factors II, VII, IX and X [13].

4. Vitamin K would transform polypeptide precursors in a still unknown way into active clotting factors [1, 6].

Hepatic injury diminishes the activity of the factors produced in the liver, and the resulting coagulation defect is resistant to vitamin K therapy. In the case of normal liver function, vitamin K deficiency decreases the activity of factors II, VII, IX and X, whereas the level of factors V, VIII and XII remains normal. When the synthesis or absorption of vitamin K is affected, parenteral supplementation can normalize blood clotting. Defective synthesis or absorption can be differentiated by oral administration of vitamin K, as in the latter condition it remains obviously ineffective.

The above considerations suggest that the reduced level of clotting factors in children with cyanotic heart disease can be ascribed to several factors, even when the possibility of consumption owing to increased intravascular clotting and secondary fibrinolysis can be excluded. In the majority of the cases examined, the activity of clotting factors increased on intramuscular but not on oral administration of vitamin K, indicating a defective absorption from the intestines. In some cases, however, even intramuscular vitamin K had no effect. This, together with a decreased level in some patients of factor V, the synthesis of which does not depend on vitamin K, suggests that impaired liver function contributes to some extent to the coagulopathy in these patients.

Defective absorption and liver function can equally be explained

by the haemodynamic state of the patients, the slowing down of circulation, the congestion, the reduced arterial oxygen saturation, and the tissue hypoxia.

It may be asked whether it is necessary to increase the subnormal level of protein clotting factors by parenteral vitamin K administration. As it was shown earlier [4], the Quick-value and factors of the prothrombin-complex rarely fall below 20—25%. A similar decrease — without the simultaneous effect of other factors — will not lead to spontaneous bleeding. On the other hand, the slower circulation, the increased blood viscosity and acidosis of these patients with secondary polyglobulia will shift the haemostatic balance rather toward thrombosis. The decreased synthesis of clotting factors seems to act in restoring the disturbed balance.

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