ANTAGONISM OF ANTICOAGULANTS DICOUMAROL, TROMEXAN, AND PHENYLINDANDIONE BY VITAMIN K₁

BY

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There are many conflicting opinions on the value of water-soluble preparations of vitamin K in overcoming prothrombin deficiency induced by dicoumarol. On the one hand, James *et al.* (1949) stated that water-soluble preparations (menadione (menaphthone B.P.) and "synkavit"), in large doses intravenously, had little effect in shortening the prothrombin time after dicoumarol therapy. Miller *et al.* (1950) came to the same conclusions.

On the other hand, in contrast to these reports, Overman and his associates (1951) found that water-soluble preparations of vitamin K were effective in overcoming the excessively prolonged prothrombin times encountered in dicoumarol therapy. In criticism of James's reports, Overman *et al.* state that the large amounts of dicoumarol given in James's experiments may have significantly altered the response to water-soluble vitamin K. In addition, they thought that the fact that in Miller's experiments the dicoumarol and vitamin K were administered simultaneously probably altered the response to the vitamin K.

In my experience water-soluble preparations of vitamin K, given in large doses of 200–600 mg. intravenously, have only a very limited effect in reducing the prothrombin times in patients receiving dicoumarol. Patients sensitive to dicoumarol will often have a sudden marked rise in the prothrombin time in the early days of treatment. In most of these the withholding of dicoumarol will result in a rapid fall in the prothrombin time. Administration of water-soluble vitamin K will in many cases hasten the fall in the prothrombin time, though this response is not always to be relied upon. In addition, I have found that water-soluble preparations will in many cases produce an appreciable

fall in the prothrombin time in patients in whom dicoumarol has been stopped for several days, provided that the initial doses of dicoumarol were not excessive. I believe that the water-soluble preparations of vitamin K are effective only when most of the dicoumarol has already been excreted. This is supported by Overman's experiments, in which the average dose of dicoumarol was only 403 mg. and in half of the cases no dicoumarol had been given in the 48 hours before the administration of water-soluble vitamin K. In those cases in which dicoumarol was given in the 24 hours preceding the administration of vitamin K, the prothrombin time (when it was stated) rose suddenly from a therapeutically safe level to a dangerously high level within 24 hours. This sudden rise in 24 hours after small or average doses of dicoumarol represents the reaction of the sensitive patient who will often respond to the withholding of dicoumarol alone. In the one case in Overman's series in which the prothrombin level was below 10% of normal on two successive days, and in which dicoumarol had been given within the 24 hours before the administration of vitamin K, there was no response to water-soluble vitamin K.

Vitamin K₁

In contrast to the lack of response to water-soluble preparations of vitamin K, both James and Miller noted an effective response to intravenous doses of 500 mg. of vitamin K₁ oxide and vitamin K₁. Miller found that vitamin K₁ was more effective than vitamin K₁ oxide. In a more recent report, Fuller and Barker (1951) concluded that an oral dose of 500 mg. of vitamin K₁ was a satisfactory dicoumarol antagonist, significantly reducing the prothrombin time 20 hours after the administration of vitamin K₁.

To assess the value of vitamin K₁, given orally, 500 mg. was administered to seven patients on dicoumarol, four patients on "tromexan," and seven patients on the more recently introduced anticoagulant phenylindandione. (This last drug has an effect midway between that of dicoumarol and that of tromexan.) In nearly all the cases, average or large doses of the anticoagulant drugs were given to produce a severe prothrombin deficiency in the region of 10% or below on at least two successive days (Case 3 is the one exception). With the thromboplastin used in this study, prothrombin times of 35 seconds and 50 seconds represent prothrombin levels of 20% and 10% of normal respectively. Six cases of the series (5, 7, 13, 14, 17, and 18) had severe

TABLE 1.—Response to 500 mg. Vitamin K₁ Orally in Patients on Dicoumarol

Case	Age		K Day—2	K Day—1	K Day	Prothrombin Times—Hours after K ₁					Expected P.T. at 20 hrs.	Hours between Last Dose of Dicoumarol and Vit. K ₁	Total Dicoumarol Given
						4 hrs.	6 hrs.	8 hrs.	12 hrs.	20 hrs.			
1	68	P.T. — D. mg. — K ₁ mg. —	200	70 50	85 500 haematuria	—	—	14		15	70–85	24	550 mg. in 3 days
2	68	P.T. — D. — K ₁ —	58	60 50	60 500		20		18		50–60	23	600 mg. in 7 days
3	56	P.T. — D. — K ₁ —	200	600	110 500	54		23		19	110+	6	800 mg. in 2 days
4	64	P.T. — D. — K ₁ —	50	58 50	65 100 500			21		18	80–100	†	850 mg. in 6 days
5	72	P.T. — D. — K ₁ —	70 200	120 50	160 500 haemorrhage	120			47	26	120+	19	800 mg. in 5 days
6	60	P.T. — D. — K ₁ —	43 100	44 150	65 100 500	40		21		16	65	1	1,200 mg. in 8 days
7	58	P.T. — D. — K ₁ —	80 200	75 200	100 100 500		59	28		16	120+	8	1,850 mg. in 11 days

P.T.—Prothrombin time in seconds. D.—Dicoumarol. Expected P.T.—Approximate expected prothrombin time if no K₁ had been given.

TABLE II.—Response to 500 mg. Vitamin K₁ Orally in Patients on Phenylindandione (P.I.D.)

Case	Age		K Day - 2	K Day - 1	K Day	Prothrombin Times—Hours After K ₁					Expected P.T. at 20 hrs.	Hours Between Last Dose of P.I.D. and K ₁	Total P.I.D. Given
						4 hrs.	6 hrs.	8 hrs.	12 hrs.	20 hrs.			
8	63	P.T. — P.I.D. mg. — K ₁ mg. —	—	45	50	34		19		18	50	1	1,650 mg. in 15 days
9	70	P.T. — P.I.D. mg. — K ₁ mg. —	34	44	52	32	23			18	30-35	16	1,250 mg. in 10 days
10	71	P.T. — P.I.D. mg. — K ₁ mg. —	100	150	58	44		21		20	50	1	1,550 mg. in 15 days
11	85	P.T. — P.I.D. mg. — K ₁ mg. —	58	60	85	31		23		22	75-85	2	1,400 mg. in 9 days
12	86	P.T. — P.I.D. mg. — K ₁ mg. —	55	60	93	55		27		14	95+	4	1,150 mg. in 6 days
13	61	P.T. — P.I.D. mg. — K ₁ mg. —	72	90	110	80	31	22	22	21	100+	5	1,150 mg. in 6 days
14	86	P.T. — P.I.D. mg. — K ₁ mg. —	85	110	120	150	47	43	33	23	120+	10	1,700 mg. in 8 days

P.T. = Prothrombin time in seconds. Expected P.T. = Approximate expected prothrombin time if no K₁ had been given.TABLE III.—Response to 500 mg. Vitamin K₁ Orally in Patients on Tromexan

Case	Age		K Day - 2	K Day - 1	K Day	Prothrombin Times—Hours After K ₁					Expected P.T. at 20 hrs.	Hours Between Last Dose of Tromexan and K ₁	Total Tromexan Given
						4 hrs.	6 hrs.	8 hrs.	12 hrs.	20 hrs.			
15	62	P.T. — T. mg. — K ₁ mg. —	—	55	62			30		20	50-60	1	4,800 mg. in 15 days
16	64	P.T. — T. mg. — K ₁ mg. —	47	57	66	26		19		17	60-70	1	4,800 mg. in 6 days
17	53	P.T. — T. mg. — K ₁ mg. —	60	95	115	75		24		17	80-90	6	6,300 mg. in 6 days
18	61	P.T. — T. mg. — K ₁ mg. —	67	95	95	80		22		14	65-80	6	5,700 mg. in 6 days

P.T. = Prothrombin time in seconds. T. = Tromexan. Expected P.T. = Approximate expected prothrombin time if no K₁ had been given.

prothrombin deficiencies, with times of 75 seconds and over on at least two successive days. In three cases (5, 13, and 18) anticoagulant drugs were persisted with in order to produce haemorrhage, and, in addition, microscopical haematuria was noted in a further case (Case 1).

To eliminate any appreciable fall that might result merely from stopping anticoagulant drugs, all the cases had the last doses of the anticoagulant less than 24 hours before receiving vitamin K₁. In 14 of the 18 cases the longest interval between the administration of anticoagulants and vitamin K₁ was 10 hours, with an average of 3½ hours.

Tables I to III show the responses to oral vitamin K₁ in these 18 patients. In all cases the prothrombin time fell to a safe level within eight hours, and if in each case the prothrombin time had been taken six hours after vitamin K₁ had been given it would probably have been found that a safe prothrombin level of above 10% had been reached in six hours in nearly all. (One exception is Case 7, in which the prothrombin time was 59 seconds at six hours, representing a level of approximately just below 10%.) The prothrombin times in all cases had fallen to 26 seconds or below within 20 hours.

Fig. 1 shows the dramatic response to vitamin K₁ in the four most severe cases, including the three in which frank haemorrhage occurred.

FIG. 1

FIG. 2

FIG. 1.—The response to 500 mg. of vitamin K₁ given orally, in four cases with severe prothrombin deficiencies, including frank haemorrhages in three cases. FIG. 2.—Shows the superiority of vitamin K₁ compared with water-soluble vitamin K (synkavit) in counteracting the prothrombopenic action of large doses of dicoumarol in two cases.

In two cases (7 and 14) a "rebound phenomenon" occurred. In Case 7 very large doses of dicoumarol had been given in the three or four days before vitamin K₁ was administered, and a prothrombin level of below 10% of normal was present on three days. After, however, the prothrombin time had fallen to normal (16 seconds) within 20 hours of the administration of vitamin K₁, it gradually rose to 22, 29, and 36 seconds in the next three days. A further dose of 500 mg. of vitamin K₁, orally, restored the prothrombin time to normal, with no further rise. Similarly, in Case 14, after excessive doses of phenylindandione, resulting in a prothrombin level of well below 10% of normal for three days before vitamin K₁ was given, the prothrombin time fell to 23 seconds (a level of approximately 40%) within 20 hours, only to rise again to 27 and 31 seconds in the next two days. One further dose of 500 mg. of vitamin K₁ was sufficient to restore and maintain the prothrombin time at normal.

Comparison Between Water-soluble Vitamin K and Vitamin K₁

To assess the relative effects of water-soluble vitamin K and vitamin K₁ the following experiments were carried out (see Fig. 2). 1,100 mg. of dicoumarol was given to each of two cases over a period of four days. At the same time 500 mg. of synkavit (a water-soluble preparation of vitamin K) was given daily in two doses of 250 mg. intramuscularly. (Owing to the toxic reactions it was not possible to give such large doses of synkavit intravenously.) As can be seen from Fig. 2, the simultaneous administration of synkavit and dicoumarol did not prevent the prothrombotic effect (although there is no doubt that the synkavit had some antagonistic effect, as without that substance one would have expected higher prothrombin times after such large doses of dicoumarol). On the fifth day 500 mg. of vitamin K₁ was given by mouth, and at the same time 600 mg. of dicoumarol (that is, double the dose given with synkavit). In 24 hours the prothrombin time had fallen from the region of 45 seconds to near normal—16 and 18 seconds. On each of the next two days 600 mg. of dicoumarol was given, with 500 mg. of vitamin K₁, and in spite of such large doses of dicoumarol the prothrombin times remained normal. In all, both cases had received 2,900 mg. of dicoumarol. On the eighth and ninth days the prothrombin times rose again, and a further 500 mg. of vitamin K₁ given on the ninth day once more restored the prothrombin times to normal by the following day. On the eleventh day the prothrombin times in both patients had risen again, and 500 mg. of synkavit failed to prevent the prothrombin time rising still higher on the twelfth day. A further dose of 500 mg. of vitamin K₁ on the twelfth day was needed to restore the rising prothrombin time to normal. It was not until 14 days after the last dose of dicoumarol that the prothrombin remained normal.

FIG. 3.—Shows the superiority of vitamin K₁, compared with water-soluble vitamin K (synkavit) in counteracting the prothrombotic action of large doses of tromexan.

The above experiment shows the remarkable effect of vitamin K₁ in both preventing and counteracting the prothrombotic effect of dicoumarol even after very large doses, whereas the water-soluble preparations of vitamin K had only a partial preventive effect. In addition, it shows the failure of water-soluble vitamin K to reduce the prothrombin time when any appreciable quantity of dicoumarol still remains in the body.

One further point can be noted from the above experiments. After very large doses of dicoumarol the drug may remain stored in the body for as long as 14 days. To overcome the effect of stored dicoumarol, repeated doses of vitamin K₁ are needed.

An experiment similar to the above was carried out in two patients when tromexan was used as the anticoagulant drug. Figs. 3 and 4 show the much greater effect of vitamin K₁ compared with that of water-soluble vitamin K. In contrast to the experiments with dicoumarol, no rebound phenomenon occurred, because tromexan is excreted so much more rapidly than dicoumarol. Unfortunately, supplies of the anticoagulant phenylindandione were insufficient to carry out similar experiments.

Conclusion

It is apparent that vitamin K₁ is most effective in overcoming the prothrombin deficiency induced by such drugs as dicoumarol, tromexan, and phenylindandione. Even with very severe deficiencies, resulting in prothrombin levels of below 10% for several days, an oral dose of 500 mg. of vitamin K₁ will restore the prothrombin time to a safe level within eight hours, the effect being evident within four hours. The effect was also noticed even when congestive failure was present.

In three cases with frank haemorrhagic manifestations vitamin K₁ stopped bleeding within a few hours, and no transfusions were necessary.

When very large doses of dicoumarol (and to a lesser extent phenylindandione) have been given, with the consequent storage of the drug in the body, repeated doses of vitamin K₁ may be needed to prevent a further rise in the prothrombin times—"rebound phenomenon." This effect does not occur with tromexan owing to the rapidity of excretion of the drug.

Comparison of the effect of water-soluble preparations of vitamin K with that of vitamin K₁ leaves no doubt that the latter should be the drug of choice when it is essential to overcome a severe prothrombin deficiency, particularly if bleeding is present. In the latter event, unless there are also signs of shock due to the lack of blood, it should not be necessary to resort to blood transfusions. The availability of vitamin K₁ should widen the scope of anticoagulant therapy with dicoumarol and allied drugs, so long as it is

FIG. 4.—A similar experiment to that of Fig. 3.

remembered that prothrombin estimations are essential for their control. The possibility of an urgent operation being necessary in a patient on dicoumarol or allied drugs has always been a drawback to their use. This drawback is largely overcome by the use of vitamin K₁.

In considering the use of such a potent drug as vitamin K₁ it must be remembered that the prompt restoration of the prothrombin to a normal, or near normal, level in a patient requiring the use of anticoagulants will inevitably restore the dangers of thrombo-embolism. Vitamin K₁ must therefore be used with caution and only in cases where the danger of severe prothrombin deficiency overrides that of thrombo-embolism. This statement applies to the doses of vitamin K₁ used in this report. Further work is in progress with smaller doses of vitamin K₁, which it is hoped will overcome a dangerous prothrombin deficiency that may arise from anticoagulant therapy but will not restore the prothrombin to a level where thrombo-embolism is likely.

In using large doses of vitamin K₁ it must also be remembered that the patient may become refractory to anticoagulants and require much larger doses of the anticoagulant drug after the administration of the vitamin.

Summary

In 18 patients, vitamin K₁, in a single oral dose of 500 mg., was completely effective in restoring a safe prothrombin level after a severe and prolonged prothrombin deficiency due to such anticoagulant drugs as dicoumarol, tromexan, and phenylindandione.

This effect was evident within eight hours, and the action of the vitamin was apparent within four hours.

In three cases of frank haemorrhage due to anticoagulant drugs, an oral dose of vitamin K₁ was in itself sufficient to stop bleeding in a matter of hours.

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Nation-wide hunts for donors of rare types of blood should no longer be necessary with the coming into use this week of a national panel of nearly 2,000 donors whose red blood cells have been classified down to the finest subdivisions of the blood groups. Several hundred distinguishable kinds of blood are included in the panel. The preliminary testing and selection of donors for the panel was done by the regional transfusion centres of the National Blood Transfusion Service, the Scottish National Blood Transfusion Association, and the Northern Ireland Blood Transfusion Service. The Blood Group Reference Laboratory, run on behalf of the Ministry of Health by the Medical Research Council, was responsible for the detailed testing and classification. The testing of the donors and the classifying and checking of the results have occupied several members of the laboratory staff for about a year. The register will be kept up to date by replacing any donor who resigns by a new donor. The regional transfusion centre in whose region the resigning donor lives will be responsible for replacing him, and the Blood Group Reference Laboratory will carry out the necessary detailed tests and issue periodical amendments to the register. No other country has a panel of donors in any way comparable with this one, which has only become possible through the unique organization of the National Blood Transfusion Services and the leading position which this country holds in blood-group research and technology.

STUDIES IN PRE-DIABETES

BY

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PART I

ITS INCIDENCE IN THE CAPE, ITS EARLY DETECTION, AND THE CONCEPT OF THE PRE-DIABETIC FATHER

Coming events cast their shadows before. The woman destined to develop diabetes divulges her future fate by producing infants which are dead,¹⁻⁷ or large,^{1,8,11-12} by rapid obesity during pregnancy,^{6,8,11,12} and perhaps by overlactation.¹² The only dissentient voice has been that of Herzstein and Dolger,¹³ and their figures are of doubtful validity.¹

Observations on Pre-diabetic Women

The high foetal loss rate and, particularly, the macro-infantia are applicable to pre-diabetic women in the Cape, both white and "coloured" (mixed race), and probably African also.

Method.—The method of personal questioning of unselected consecutive patients which was adopted is admittedly subject to great inaccuracy. For controls we took a series of cases of similar race and age distribution who were attending hospital for various reasons, none of them being known diabetics. As there is no reason to believe that diabetics are greater exaggerators of birth size than other hospital patients, conclusions drawn from a comparison of the two groups should be valid. Absolute figures, however, cannot be regarded as accurate. Babies are included in the survey only when the mothers knew their weight with reasonable and credible accuracy. "Large" was not considered good enough, nor "I'm sure he was over 10 lb.," unless the latter was confirmed by definite memory of the use of a scale and suitable remarks by doctor or midwife. Whenever a large baby was claimed every verbal effort was made to obtain confirmatory evidence before acceptance.

"Stillbirths" here include deaths within 48 hours of birth, and their recorded percentages are also subject to inaccuracies.

Large Babies

Table I shows that 62% of the women who develop overt diabetes after child-bearing claim to have had at least one baby over 10 lb. (4.5 kg.) in weight. This compares with

TABLE I.—Pre-diabetic and Control Mothers

	Total Mothers		Mothers with at Least 1 Child over 10 lb.		Mothers with No Child over 8 lb.		Mothers with at Least 1 Stillbirth	
	P.	C.	P.	C.	P.	C.	P.	C.
White	50	50	31	7	2	23	8	4
Coloured	50	50	31	5	6	30	22	9
Total	100	100*	62%	12%	8%	53%	30%†	13%†

P = Pre-diabetic. C = Control.

* Total number of control mothers was actually 130—reduced to 100 for easy comparison.

† Difference between these two proportions is two and a half times its standard error.

Kriss and Futcher's⁹ 58% and the figures of Miller¹ and Moss and Mulholland.⁷ So commonly is there a story of several large babies, sometimes with stillbirths, that we have come to regard this as strongly confirmatory of diabetes in a doubtful new case, so that necessary treatment may be started without awaiting the results of chemical analyses.