Studies on the Anticoagulant Phenylindanedione

I. The Effect of Emulsified Vitamin K_1 on Phenylindanedione-Induced Hypoprothrombinemia

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PHENYLINDANEDIONE, a drug developed by certain French workers because of a more transitory prothrombopenic action than dicoumarol,[1, 2] has been used extensively as an anticoagulant for the past eighteen months at the Boston City Hospital.[3] While phenylindanedione is known to be an effective drug in the production of hypoprothrombinemia,[4] an objection to its clinical use has been the concept that the hypoprothrombinemic state is not counteracted by vitamin K active compounds.[2, 5, 6]

Stimulated by the success of intravenous emulsified vitamin K_1 as an antagonist to the hypoprothrombinemia induced by dicumarol,[8] Tromexan[9] and anticoagulant ✱63,[10] studies have been undertaken to investigate intravenous emulsified vitamin K_1 as an antagonist to the prothrombopenic action of phenylindanedione.

Methods

1. Six random patients who had received phenylindanedione* in dosages sufficient to increase their prothrombin times to levels ranging from 31.5 to 65 seconds were administered a vitamin K_1 emulsion intravenously in doses from 2 to 10 mg. per Kg. body weight. One and two-stage methods of plasma prothrombin assay, and glass and silicone clotting times were determined before and after injection of the emulsion at the intervals indicated in table 1.

2. Six individuals were administered preliminary amounts of intravenous emulsified vitamin K_1 in doses of 25 and 50 mg. to note its effect upon subsequent dosages of phenylindanedione as indicated in table 2.

3. Six patients who developed hemorrhagic complications during therapy with phenylindanedione, were administered intravenous emulsified vitamin K_1 in dosages ranging from 1 to 10 mg. per Kg., as indicated in table 3.

The emulsion used† contained 50 mg. of vitamin K_1 per cu. ml. and was injected intravenously through a number 20 needle over intervals varying from 30 seconds to 10 minutes. The phenylindanedione was administered orally in 50 mg. tablets at 12 hour intervals.

Prothrombin assays were obtained by Quick's method[11] on undiluted plasma using dried rabbit brain thromboplastin (Difco) and 0.01 molar calcium chloride. The controls ranged between 13 and 15 seconds. These were frequently checked by the one-stage method of Owren[12] and the two-stage assay of Ware and Seegers.[13] Silicone clotting times were obtained in tubes coated with Drifilm,[14] normal values being 40 to 80 minutes. Glass clotting

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times were done by a two-tube modification of the Lee-White method, normal values being 7 to 14 minutes.

Results

The data in table 1 reveal that all patients with phenylindanedione-induced hypoprothrombinemia manifested a prompt decline in the prothrombin times following administration of intravenous emulsified vitamin K_1. When a dose of either 5 or 10 mg. per Kg. was employed, the prothrombin times declined to below 20 seconds in 120 minutes despite the initial level. After 180 minutes, the prothrombin times were within a relatively normal range (13.1 to 15.8 seconds). In one patient (E. B.), who received 2 mg. per Kg., the restoration of the prothrombin time was not as dramatically rapid.

In 2 patients in whom specimens for prothrombin times were obtained every 15 minutes, a variable effect was noted in the first 30 minutes. By the first 60 minutes, however, a distinct return of the prothrombin times toward normal had occurred.

TABLE 1.—*The Response of the Prothrombin Time (Quick) to Intravenous Emulsified Vitamin K_1 in 6 Patients with Phenylindanedione-Induced Hypoprothrombinemia*

Patient	Vitamin K_1 mg./Kg.	Initial	Prothrombin Time in Seconds (Quick) after vitamin K_1 administration							
			15 min.	30 min.	60 min.	90 min.	120 min.	180 min.	6 hr.	24 hr.
H. J.	10	34	28.4	21.4	19.3	16	16	13.1	13	
E. O.	10	44	38.8	40.8	19	18	18	16.3	14	
W. L.	10	40.6					19.8	16.8		16
F. R.	10	31.5					18.6	15.1		15
F. M.	5	65			22.7		17.2	14.1		14
E. B.	2	28.5			26.9		22.8	22	18.8	13.4

A representative response to the vitamin K_1 emulsion is demonstrated graphically in figure 1. For comparison, a recovery curve was obtained with the use of intravenous menadione sodium bisulfite (10 mg. per Kg.), as well as the spontaneous recovery from the prothrombopenic action of phenylindanedione. The recovery both spontaneously and with menadione bisulfite revealed closely parallel results, since 48 hours elapsed before relatively normal prothrombin times ensued. It would appear, therefore, that the menadione bisulfite exerted essentially no antagonism to the hypoprothrombinemia induced by phenylindanedione.

In figure 2 is recorded the effect of vitamin K_1 emulsion on phenylindanedione-induced hypoprothrombinemia as manifested by the Quick, the Owren and the two-stage methods of plasma prothrombin assay and the glass and silicone clotting times. While there was a slight prolongation of the glass clotting time to 19 minutes prior to the administration of vitamin K_1 emulsion, in 2 hours normal glass clotting times were obtained. Although the silicone clotting time showed a decline after administration of emulsified vitamin K_1, the fall lagged somewhat behind the restoration of prothrombin such that 3 hours following vitamin K_1 injection the silicone clotting time was prolonged to 10 hours even though the prothrombin determinations were close to normal by then. Fibrinogen levels were determined and found to be unaltered.

The inhibition of the prothrombopenic action of phenylindanedione by emulsified vitamin K_1 is demonstrated in table 2. Preliminary amounts of emulsified

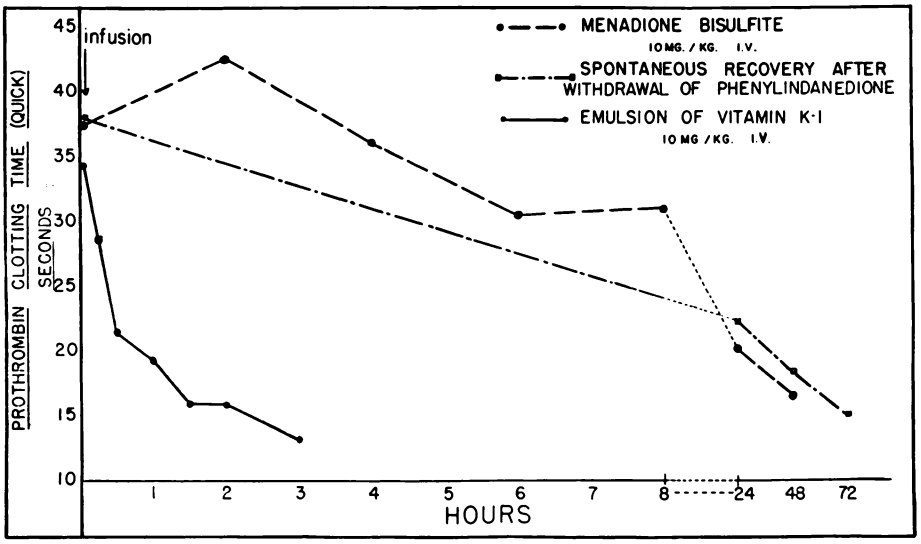

FIG. 1.—The effect of an intravenous emulsion of vitamin K_1 on phenylindanedione-induced hypoprothrombinemia.

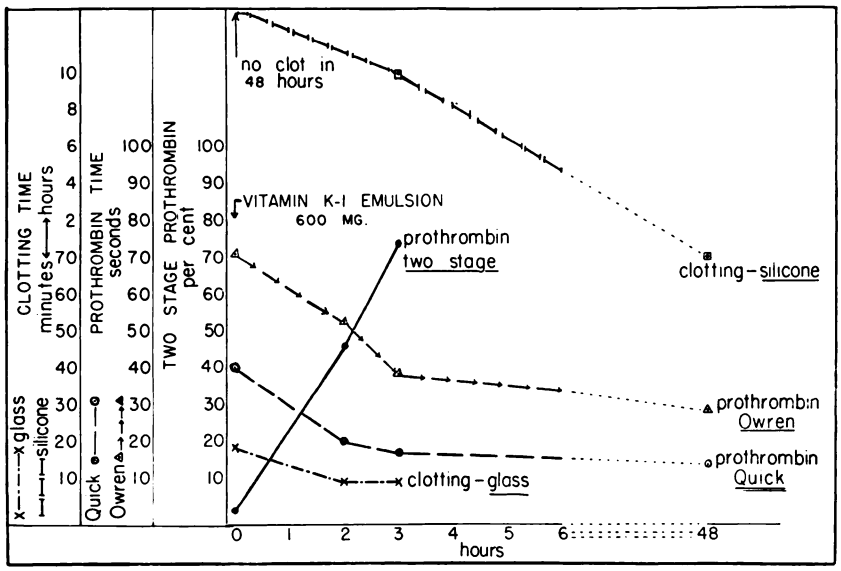

FIG. 2.—The effect of an intravenous emulsion of vitamin K_1 on phenylindanedione-induced hypoprothrombinemia.

vitamin K_1 (as little as 25 mg. intravenously) prevented subsequent induction of the hypoprothrombinemia with phenylindanedione. In spite of the administration of twice the average daily dose of this anticoagulant, the inhibition persisted for three days as manifested by the relatively normal Quick and two-stage plasma

prothrombin assays. Usually such doses of phenylindanedione would have resulted in attaining the therapeutic range (Quick prothrombin time between 25 and 35 seconds) within 36 hours.

TABLE 2.—*The Inhibition of Phenylindanedione-Induced Hypoprothrombinemia by Intravenous Vitamin K_1 Emulsion*

Patient	Date	Vitamin K_1 i.v. in mg.	Phenylindanedione Daily Dose in mg.	Prothrombin Time (Seconds) (Quick)	Two Stage Prothrombin (per cent)
M. R.	1-28	25	300	14.3	
	1-29		200	15.1	
	1-30		200	15.4	
	1-31			15.2	
E. M.	1-28	25	300	14.6	77
	1-29		200	18.9	74
	1-30		200	20.3	74
	1-31			23	50
J. W.	2-4	25	300	14	87
	2-5		200	14.2	92
	2-6		200	14.1	93
	2-7		200	15.5	88
	2-8			16.8	69
C. S.	2-4	25	300	14	100
	2-5		200	14.8	93
	2-6		200	15	92
	2-7		200	15	92
	2-8			16.8	80
C. J.	2-11	50	400	14.8	100
	2-12		400	15.2	100
	2-13	50	400	17	74
	2-14		400	15.7	82
	2-15		400	14.8	86
	2-16		400	17.7	74
F. B.	2-11	50	400	15	82
	2-12		400	15.9	86
	2-13		400	17.4	74
	2-14	50	400	20.2	48
	2-15		400	15.7	82
	2-16		400	17.2	74

The third group of patients (table 3) studied had developed hemorrhagic complications during therapeutic doses of phenylindanedione. Of the 4 cases who developed melena, 2 had asymptomatic chronic duodenal ulcers as demonstrated by subsequent roentgenographic studies. The other 2 patients were not investigated by gastro-intestinal x-ray studies. Patient (B. L.) with a hemothorax had been placed on anticoagulant therapy following the onset of a thrombophlebitis associated with a traumatic injury. A roentgenogram of the chest later revealed unsuspected rib fractures. Patient (M. C.) with hemoptysis had been receiving

phenylindanedione on an ambulatory basis because of embolic phenomena associated with mitral stenosis and chronic auricular fibrillation. The hemoptysis ceased three hours following K_1 intravenously (2mg./Kg.).

The response of the Quick prothrombin times to the intravenous vitamin K_1 emulsion in this group was not as dramatically rapid as the response in the experimental non-hemorrhagic group (Table I). Within two hours of the administration of the vitamin K_1 emulsion, the Quick prothrombin times were all above 20 seconds. In six hours, the three specimens obtained were 20 seconds or below; in 24 hours all determinations were below 20 seconds. The hemorrhagic complications, however, abated apparently prior to the restoration of the prothrombin times.

TABLE 3.—*The Response of the Prothrombin Time to Intravenous Emulsified Vitamin K_1 in 6 Patients Who Developed Hemorrhagic Complications Subsequent to Therapy with Phenylindanedione*

Patient	Hemorrhagic Complications	Vitamin K_1 Mg./Kg.	Initial Level	Prothrombin Time in Seconds (Quick)					
				1 hr.	2 hrs.	6 hrs.	24 hrs.	48 hrs.	72 hrs.
C. B.	Melena (4+ guaiac)	10	34 (3%)*		24.4 (24%)*		18.6 (27)*	17.8	15 (69%)*
B. L.	Hemothorax	10	40.2			20	19.3		
J. H.	Melena (4+ guaiac)	5	33				19.5	19	
C. J.	Melena (4+ guaiac)	5	31		22	18.4	16.1	13.6	
M. C.	Hemoptysis	2	41	39	33.2		18.5	15	
T. C.	Melena (3+ guaiac)	1	30			15.9	15		

* The figures in parentheses indicate two-stage prothrombin assay.

DISCUSSION

These studies, contrary to previous concepts, indicate that phenylindanedione-induced hypoprothrombinemia is readily counteracted by intravenous emulsified vitamin K_1. With the administration of 5 or 10 mg. per Kg. of vitamin K_1 emulsion in one injection, restoration of the prothrombin time to relatively normal range occurred in 180 minutes. These results were produced consistently independent of the speed of intravenous administration which varied from 30 seconds to 10 minutes. No systemic reactions to the emulsion were observed.

Since the 10 mg. per Kg. doses failed to effect a more rapid restoration of the prothrombin times, the 5 mg. per Kg. doses were considered to be optimal, the larger doses producing a longer refractoriness to subsequent prothrombopenic agents. Hypoprothrombinemia could not be induced even after three weeks of phenylindanedione administration in patient E. B. who had received 10 mg. per Kg. of the vitamin K_1 emulsion. With the use of 2 mg. per Kg. of K_1 emulsion a refractory period of eight days was encountered; however, this dose was unsatisfactory when the speediest effect was desired. A ten day refractory period may be anticipated when a dose of 5 mg. per Kg. is employed. If subsequent anticoagulant therapy becomes necessary during such a refractory state, the use of a heparin-like anticoagulant is required. Further study of this problem demonstrated that a dose as small as 25 mg. of the emulsified vitamin K_1 given intra-

venously inhibited the prothrombopenic action of twice the average daily dose of phenylindanedione for three days. One subject (B. B.) has been refractory to customary doses of phenylindanedione thirty days after the last dose of 900 mg. was given in divided doses orally over the course of nineteen days for experimental purposes. For this reason, smaller doses (0.5 to 2 mg. per Kg.) should be used for simple hypoprothrombinemia without hemorrhage or even with hemorrhage which is not an emergency. Thus the main objection to the use of phenylindanedione is no longer tenable. In fact, phenylindanedione-induced hypoprothrombinemia has been counteracted more rapidly than that of any prothrombopenic agent employed thus far.[7-9]

Summary

1. Phenylindanedione-induced hypoprothrombinemia is rapidly counteracted by a vitamin K_1 emulsion. This hypoprothrombinemia is antagonized at a more rapid rate than that induced by any of the other commonly employed prothrombopenic agents.

2. The optimum dose of the vitamin K_1 emulsion in emergency is 5 mg. per Kg. Since a refractoriness to the prothrombopenic action of phenylindanedione ensues, smaller doses should be used in situations where there is no emergency.

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