obvious and at the same time tend to enlarge. They are only rarely associated with any respiratory disturbance, and it is surprising how well an infant may be with large cysts in his lung. We do not think it necessary to continue antibiotics until the cysts disappear, and it is our practice to cease treatment when the child is clinically well and the temperature normal.

In a disease which causes such extensive lung changes one would expect sequelae in the form of chronic pulmonary suppuration, but, in the children who survived, the ultimate return of the x-ray films to normal and the invariably normal development of the patient were most gratifying. Bronchograms did not seem to be indicated, and were therefore not done.

Summary

The literature on staphylococcal pneumonia is reviewed briefly. Attention is drawn to an apparent increase in frequency of the disease and its high mortality.

A series of 55 cases in children under the age of 2 years, occurring during a period of 29 months, are discussed. Eleven of them were associated with chronic debilitating disease, the pneumonia being a terminal event (group A). The remaining 44 cases (group B) are discussed in detail with reference to diagnosis, x-ray changes, treatment, and prognosis. Ten patients died—a mortality of 23%.

The relative ineffectiveness of the broad-spectrum antibiotics in controlling the infection is stressed, and the high percentage of penicillin-resistant organisms is noted (92%).

Empyema or pneumothorax was present in 28 cases (64%). Emphasis is laid on the importance of surgical treatment when these complications occur.

Cysts were present in 29 cases (66%).

Follow-up x-ray examinations in 29 out of the 34 survivors showed nothing abnormal, there being no residual signs or symptoms.

APPENDIX: TECHNIQUE FOR INTERCOSTAL DRAINAGE

Apparatus.—Exploring trocar (Allen and Hanburys No. 16920). Jaques catheter, sizes 3–6. Glass connexion and rubber tube for attaching catheter to Woulfe bottle with underwater seal. A small electric suction-pump facilitates drainage. For this purpose we use a low-pressure pump made by the Genito-Urinary Company.

Method.—After locating the site for drainage—a good lateral x-ray film of the chest is essential for this—the skin is infiltrated with a local analgesic. A nick is then made with a scalpel, and the trocar and cannula are inserted quickly into the chest. After withdrawing the trocar the catheter is passed through the cannula, which is then carefully removed. The catheter is then connected to the suction apparatus, approximately 2 in. (5 cm.) being left inside the chest. For small infants a cannula of 9–14 Charrière gauge is satisfactory. Speed is important, as the operation is distressing and the baby may be *in extremis* when it is performed.

We wish to thank the members of the honorary medical staff for allowing us to publish details of cases under their supervision, and Mr. R. Plummer for preparing the photographs.

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EFFECT OF INTRAVENOUS VITAMIN K₁ ON THE ACTION OF PHENINDIONE

BY

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Vitamin K₁ (2-methyl-3-phytyl-1:4:naphthoquinone) when administered orally has been shown to have an antagonistic effect on the action of phenindione (2-phenylindane-1:3-dione) (Toohey, 1952; Perlick, 1953; Chalmers *et al.*, 1954). Because the vitamin is fat-soluble, preparations suitable for intravenous injection have been associated with difficulties in administration (Douglas and Brown, 1952).

While preparations of vitamin K₁ suitable for intravenous administration have been used in America for some time, it is only recently that a new experimental emulsion of vitamin K₁ has become available for trial in this country. This paper records the results of tests performed on volunteers receiving phenindione ("dindevan") who were given intravenous injections of this new vitamin K₁ emulsion.

Material and Methods

1. The vitamin K₁ preparation used was a stable emulsion containing 20 mg. of vitamin K₁ per ml. It was stored in amber-coloured ampoules away from light.

2. Tests were carried out on 24 healthy volunteers, who received 5, 10, or 20 mg. of the vitamin K₁ emulsion intravenously during the administration of phenindione.

3. Using Quick's one-stage technique, "prothrombin activity" estimations were carried out by the method described by Chalmers *et al.* (1954).

4. Prothrombin was estimated by a modification of the globulin assay technique of Douglas and Biggs (1953).

5. Base-line values of prothrombin activity were determined and then phenindione was administered to the subjects for four days, by which time the prothrombin activity was of the order of 10–20%. A single intravenous injection of 5–20 mg. of vitamin K₁ was then given. At varying intervals subsequently, prothrombin activity was determined, with additional controlled tests for prothrombin itself in some of the experiments. The subjects continued to take phenindione in regular dosage until the end of the experiments.

Results

In six volunteers to whom a dose of 20 mg. of intravenous vitamin K₁ was given and in four who were given 10 mg. the prothrombin activity was raised to 100% within 24 hours irrespective of its original level (Figs. 1 and 2).

Fourteen volunteers were given 5 mg. of the vitamin (Figs. 3 and 4). In these the prothrombin activity rose from initial values of 7–19% to maximum figures of between 50 and 100%. In 10 volunteers a maximum figure was reached after 24 hours, in one after 12 hours, and in three after 6 hours.

Estimations of prothrombin activity were not made at such frequent intervals in all volunteers, as their tolerance to venepuncture was limited. However, in 19 experiments prothrombin activity was estimated three hours after dosage with vitamin K₁, and in 12 of these it showed a rise of between 5 and 26%. In seven there had been no elevation by this time. In 16 cases a six-hourly estimation was carried out—in 11 of these the level had risen by between 30 and 65% in this time; in three of the remainder it had risen by at least 14%, whilst in the remaining two there was no increase. In both of these latter patients, however, the level had risen to 100% after 24 hours.

There was no evidence that the speed of rise in prothrombin activity within the first six hours was significantly greater at the larger dose levels. In this respect 5 mg. was as effective as 20 mg. This is in accord with the findings of Cramer and Götze (1954), who used the same preparation of vitamin K₁ in doses of from 10 to 60 mg. by intravenous injection as an antidote to the longer-acting anticoagulant "marcoumar."

To determine how long a single dose of 5 mg. of vitamin K₁ continued to have an effect while anticoagulant administration was continued, the prothrombin activity was estimated in five volunteers at 48 and 72 hours (Fig. 4). At 48

hours the prothrombin activity still exceeded the initial levels by from 8 to 40%. By 72 hours the initial value had returned in three cases, and in two the value was still slightly raised.

In addition to the Quick one-stage method used in the above experiment—a method which is regarded primarily as an assay of factor VII (Donald *et al.*, 1954)—prothrombin itself was estimated in eight volunteers (see Table). In only four cases was prothrombin significantly reduced (to between 33 and 50%), and this level was raised to 100% within six hours after the administration of vitamin K₁. In three of the experiments, globulin assay for prothrombin

FIG. 1.—Effect of 20 mg. of intravenous vitamin K₁ on six subjects during administration of phenindione. Cases 6 to 11.

FIG. 2.—Effect of 10 mg. of intravenous vitamin K₁ on four subjects during administration of phenindione. Cases 12 to 15.

FIG. 3.—Effect of 5 mg. of intravenous vitamin K₁ on nine subjects during administration of phenindione. Cases 16 to 24.

FIG. 4.—Effect of 5 mg. of intravenous vitamin K₁ on five subjects during administration of phenindione. Cases 25 to 29.

FIG. 5.—Control group showing the effect on the prothrombin activity of discontinuing phenindione. Cases 1 to 5.

gave normal values before vitamin K₁ was given; while a temporary slight fall in prothrombin occurred subsequently, the values were again normal 24 hours after the injection of vitamin K₁, in spite of the continued administration of phenindione.

In a control group (Fig. 5) of five volunteers, the effects of simple discontinuance of the administration of phenindione was observed. Normal or near normal prothrombin activities were reached in four cases in 72 hours and in one case in 48 hours. It is stressed that in all the other experiments the anticoagulant was administered throughout the period of observation.

Discussion

In early studies fat-soluble vitamin K₁ or its oxide, which are oil-soluble substances, were administered intravenously, dissolved in alcohol and suspended in 1-1.5 litres of 5-10% glucose (Frank *et al.*, 1939; Davidson and MacDonald, 1943; Douglas and Brown, 1952). Because of difficulties in preparation and the large bulk of the infusion, these methods proved to be unsuitable for general use.

In America small-volume emulsions of vitamin K₁ (given intravenously) have been successfully used to correct low one-stage prothrombin times induced by phenindione (Guttas *et al.*, 1953; Gamble *et al.*, 1955). These authors found the effect of fat-soluble vitamin K₁ given intravenously to be more rapid and more certain than that of the water-soluble vitamin K analogues given by the same route. Using large doses of vitamin K₁ (5 mg. per kg. body weight), Guttas *et al.* observed a resistance to further doses of phenindione for about ten days.

The present experiments have shown that 10-20 mg. of vitamin K₁ in a new emulsion given intravenously is constantly effective in returning a lowered prothrombin activity to normal within 24 hours, even though phenindione is continued. A definite rise in prothrombin activity was observed within three hours in more than half the subjects. The effect of 5 mg. of vitamin K₁ intravenously is to produce a temporary rise in prothrombin activity, which is followed by significant resistance to subsequent doses of phenindione for 48 to 72 hours. Moderate depression of prothrombin itself, as judged by the globulin assay technique, was also corrected by the administration of this preparation of vitamin K₁ (see Table), but the effect of the vitamin on lower levels was not investigated.

Effect of Vitamin K₁ Given Intravenously on Prothrombin, as Determined by Globulin Assay

Volunteer No.	Dose of Vit. K ₁ i.v.	Prothrombin				
		Before Vit. K ₁ i.v.	Hours after Vitamin K ₁ Intravenously			
			3	6	9	24
10	20 mg.	80%	80%	100%	100%	100%
11	20 "	39%	70%	100%	100%	100%
19	5 "	33%	85%	100%	100%	100%
20	5 "	44%	65%	100%	100%	100%
21	5 "	50%	78%	100%	100%	100%
22	5 "	100%	77%	63%	72%	100%
23	5 "	100%	84%	60%	100%	100%
24	5 "	100%	84%	100%	100%	100%

The principal indications for the administration of vitamin K₁ are haemorrhage and the need for surgical intervention occurring during the administration of dicoumarol-like anticoagulants. In addition, small doses may usefully be employed to raise dangerously low prothrombin activities occurring during anticoagulant therapy. From our results in healthy volunteers it would seem that with this preparation of vitamin K₁ doses of the order of 10-20 mg. would be quite sufficient in the two major indications when phenindione has been used, and can be expected to have some effect within three hours in the majority of cases. When vitamin K₁ is used simply to raise a dangerously low level of prothrombin activity doses of not more than 5 mg. are

probably advisable if anticoagulant resistance in the subsequent days, with its danger of further thrombosis, is to be avoided.

No toxic effects have been observed during 40 intravenous injections of vitamin K₁. In another series, using a different preparation of vitamin K₁, epigastric discomfort, constriction in the chest, flushing, and sweating have been reported (Stragnell and Ware, 1954), but were attributed to too rapid administration. Vitamin K₁ should always be used with caution. Stragnell (1952) has reported two deaths following its use in cases of coronary thrombosis; one was due to a demonstrable extension of the thrombus. The manufacturers of the preparation we used recommend that not more than 2 ml. of the emulsion (containing 40 mg. of vitamin K₁) be given to one patient in any one day.

Summary

An experimental emulsion of vitamin K₁ was found to be an effective antidote to phenindione.

Doses of 10 to 20 mg. of vitamin K₁ administered intravenously were found to return the prothrombin activity to 100% within 24 hours in subjects who continued to take phenindione. These doses are also effective within 24 hours in correcting a moderate deficiency of prothrombin itself. A dose of 5 mg. caused a rise to between 50 and 100% prothrombin activity within the same period. In more than half the experiments an appreciable rise of prothrombin activity occurred within three hours.

No side-reactions were observed with the doses used.

In the treatment of haemorrhage due to phenindione, an intravenous dose of 10-20 mg. is likely to be effective. If vitamin K₁ is given simply to raise a dangerously low prothrombin activity to within the therapeutic range, the evidence presented suggests that even 5 mg. may be too large a dose if an overshoot above the therapeutic range is to be avoided.

No evidence was found that the speed of the prothrombin activity response was related to the size of the dose of vitamin K₁.

It is my pleasure to thank Dr. J. N. Marshall Chalmers for his advice and encouragement, and Mr. W. Polack for technical assistance. The emulsified preparation of vitamin K₁ which was used for injection in this study was supplied by Roche Products Limited.

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The Ministry of Pensions and National Insurance has gathered statistics about sickness and injury among the working population, mainly for the years 1952-3. These figures do not justify general publication, but the volume in which they are set out is obtainable on request from the Ministry at 10, John Adam Street, London, W.C.2. The statistics are based on medical certificates sent to the Ministry with claims to benefit. They do not include illnesses of two or three days, for which no claims are lodged, or sickness in certain persons not eligible to claim. As a measure of the incapacitating sickness of the working population they are therefore incomplete. The introduction provides such essential information as is necessary for interpreting the tables.