CLINICAL TRIAL OF PHENYLINDANEDIONE AS AN ANTICOAGULANT

BY

M. TOOHEY, M.D., M.R.C.P.*Physician, New End Hospital, London*

At present dicoumarol and ethyl biscoumacetate (*bis*-3, 3'-(4-oxycoumarinyl)-ethyl acetate; "troMexan") are the two drugs with a prothrombopenic action which are in common use as anticoagulants. Dicoumarol was the first prothrombopenic drug to come into use, but its toxic effect (due, however, in many instances to indiscriminate heavy overdosage and also to lack of proper control, including unreliable estimations of the prothrombin time) has led to severe haemorrhage in many cases. The great drawback with dicoumarol is its cumulative action, which may continue long after the drug has been stopped. This cumulative effect necessitates particularly skilled and detailed control of the drug with frequent estimations of the prothrombin time if severe haemorrhage is to be avoided. Another disadvantage with dicoumarol is the long delay, usually 48 to 72 hours, before a full therapeutic effect is reached.

Ethyl biscoumacetate has a much more rapid action than dicoumarol, a therapeutic effect usually being achieved in 18 to 24 hours. Moreover, the effect of ethyl biscoumacetate, unlike that of dicoumarol, is, owing to the rapid metabolism and elimination of the drug, almost never cumulative. The rapid inactivation of ethyl biscoumacetate, however, often makes it difficult to maintain an even therapeutic prothrombin concentration, especially in the initial stages of treatment. In addition, the wide individual variation in the reaction to ethyl biscoumacetate is another factor requiring detailed and meticulous control in every case.

In recent years a new prothrombopenic drug, phenylindanedione, has aroused interest and been the subject of clinical trial. In 1944 Kabat, Stohlman, and Smith showed that certain indanedione derivatives have a specific action in reducing the plasma prothrombin. Soulier and Gueguen (1947) reported satisfactory results from using phenylindanedione, the most active of the indanedione derivatives. Jaques *et al.* (1949) found no toxic effects from phenylindanedione in animals. Blaustein *et al.* (1950) reported their observations on the use of the drug in 53 patients, and concluded that phenylindanedione had an action similar to but more rapid than that of dicoumarol. Bjerkelund (1950) found that phenylindanedione had not only a more rapid effect but also a more uniform action than dicoumarol. In addition, Bjerkelund showed that phenylindanedione had no effect on factor V.

The present paper is a report on the use of phenylindanedione in 68 patients. Most of them were suffering from coronary thrombosis or deep venous thrombosis, and in several there was evidence of cardiac failure. Quick's one-stage method was used for estimation of the prothrombin time, and the thromboplastin was a phenol-saline emulsion prepared from human brain. Therapeutic prothrombin levels of 10-20% (or approximately twice to three times the normal prothrombin time) were aimed at.

Rapidity of Action and Recovery

In practically all cases 200 mg. of phenylindanedione (divided into two equal doses) was given in the first 24 hours, followed by 100 mg. (in two equal doses) in the next 24 hours. On this dosage only 6 cases out of the 68 failed to reach an adequate therapeutic prothrombin level in 48 hours, whilst in only one of these was the prothrombin level above 40% at this time. In many cases in which the prothrombin time was estimated at 36 hours it was found that an adequate therapeutic level had been attained by this time. In most of the 68 cases an appreciable lowering of the prothrombin concentration to 50% or below was reached by 24 hours.

The effective action of phenylindanedione passes off fairly rapidly, and therefore the risk of cumulative effects is slight except where very large doses are given. Twenty-four hours after stopping the drug there was either no change or only a small fall in the prothrombin times in those patients in whom the prothrombin had previously been maintained at a full therapeutic level (10-20%) for at least several days. Up to 36 hours after cessation of phenylindanedione there was still an appreciable effect, but between 36 and 48 hours after the last dose there was a sudden sharp drop in the prothrombin time to near normal levels. By 72 hours the prothrombin times in practically all cases had become normal or almost so.

The return to normal of the prothrombin time in patients on phenylindanedione depends (as with other similar anticoagulants) largely on the level to which the prothrombin had been depressed. The lower the prothrombin concentration, the longer it takes for a normal prothrombin content to be regained. Again, any lowering of renal function will delay the excretion of the drug. In the very few cases in which the prothrombin time failed to return to normal or near normal within 48 to 72 hours after the last dose there were signs of deficient renal function.

The absorption and recovery rates of phenylindanedione are therefore midway between those of dicoumarol and ethyl biscoumacetate. Phenylindanedione has many advantages over dicoumarol in its quicker effect and the very slight danger of cumulative action. On the other hand, although it is not as rapid in action as ethyl biscoumacetate its more prolonged effect makes it much easier to maintain a therapeutic prothrombin level over a prolonged period. Ethyl biscoumacetate is practically all metabolized and excreted within 24 hours, so that omission of the drug for only one day will result in even an excessively prolonged prothrombin time returning to normal or near normal and the drug therefore losing its therapeutic effect. This rapid inactivation, combined with the wide individual variation in the reaction to the drug, necessitates the most detailed and experienced control when ethyl biscoumacetate is used. With phenylindanedione, however, the time-lag of 36 hours before there is any really appreciable change in the prothrombin concentration allows ample time for the clinician to ascertain the prothrombin level and to readjust the dose of phenylindanedione when necessary without wide fluctuations in the prothrombin level occurring.

Dosage

The initial dosage in all 68 cases was 200 mg. (100 mg. morning and evening) the first day, followed by 100 mg. on the second day. By 48 hours the full effect of this dosage was evident, and, according to the prothrombin level then reached, it was possible to estimate with a fair degree of accuracy the further doses needed for maintenance therapy. The greater the rise in the prothrombin time by 36 to 48 hours the more sensitive the patient is to the drug and the smaller the daily maintenance dose that is required. In 44 of the 68 cases this daily maintenance dose lay between 75 and 100 mg. and in only 5 cases did it fall outside the range of 50-150 mg. (see Table). The variation

Maintenance Doses of Phenylindanedione

No. of Cases	Daily Maintenance Doses in mg.	No. of Cases	Daily Maintenance Doses in mg.
2	50	3	125
4	50-75	2	125-150
22	75	4	150
4	75-100	2	150-175
18	100	1	175
4	100-125	2	175-200

in individual susceptibility to phenylindanedione is therefore not very great and seems to be much less than with either dicoumarol or ethyl biscoumacetate.

In all cases the total daily dose of phenylindanedione was given in approximately two equal amounts morning and evening. Dividing up the total daily dose seems to give more uniform results.

Guides to Dosage

There are several factors which help greatly in estimating the required maintenance doses in individual cases. Before, however, these are considered it is necessary to stress one important point. The initial doses for the first two days should (subject to the exceptional cases mentioned below) invariably be kept constant. To give a *larger* dose than 100 mg. on the second day, solely on the result of one prothrombin estimation taken 24 hours or less after starting treatment, will lead in most cases to too high a dose being given. The *full* effect of phenylindanedione is not evident for 36 to 48 hours.

To give a *smaller* dose than 100 mg. on the second day may, however, be justifiable where the prothrombin time at 24 hours (if taken) is already within a therapeutic range. In these few cases the dose of phenylindanedione on the second day may be reduced from 100 to 75 mg.

With phenylindanedione, as with all anticoagulants of the coumarin group, the extent of individual susceptibility is most important, so that the ultimate control of therapy in all cases lies in frequent prothrombin estimations. There are, however, several factors which can help in gauging, with some accuracy, the required maintenance doses of phenylindanedione:

1. Weight is important; the heavier the patient the more likely it is that the daily maintenance doses will be on the large size—that is, 125-175 mg.
2. The more acutely ill the patient (especially cases of coronary thrombosis accompanied by severe shock) the smaller the maintenance doses of phenylindanedione that are needed. It was noticed in several cases, however, that the maintenance doses in the acutely ill patients had to be increased later on when there was an improvement in their clinical condition.
3. Age is not so important in itself, but as older people tend to be more frail they require smaller doses. The apparent age is more important than the real age.
4. Renal function is of particular importance in gauging phenylindanedione (as other anticoagulant) therapy. Deficient renal function will lead to delayed excretion of the drug, so that much smaller maintenance doses are necessary. In this series the few cases in which there was an unexpectedly sharp rise in the prothrombin time were those in which it was not realized that renal function was depressed. As the majority of patients with lowered renal function are in the older age groups, it has been found most useful to perform routine blood-urea estimations in all patients of 60 and over.

Taking all the above factors into account, it will be found that the less acutely ill robust young patients require the largest maintenance doses of phenylindanedione, whilst the seriously ill frail elderly patients need the smallest doses.

Toxic Effects

No toxic effects were noticed in this series of 68 cases and there was no case of haemorrhage. Soulier and Gueguen (1947) reported dryness in the mouth, polydipsia, polyuria, and tachycardia with phenylindanedione, but in their cases very large doses, in the neighbourhood of 700 mg. and over, were given. In a small series of seven cases of mine in which large doses of phenylindanedione were

given in order to produce a severe prothrombin deficiency far in excess of that required for therapeutic purposes, no toxic effects were noticed apart from haematuria in one case only. In most patients on phenylindanedione the urine turns a pinkish-orange colour; this is of no significance.

Antidote.—The great drawback in anticoagulant therapy with drugs of the coumarin group has up till recently been the lack of a really effective antidote. Water-soluble vitamin-K analogues have only a very limited effect in correcting a severe prothrombin deficiency. Vitamin K₁, however, even by mouth, has a most dramatic and rapid effect (within 8 to 20 hours in most cases) in overcoming the prothrombopenic action of dicoumarol, ethyl biscoumacetate, and phenylindanedione (Toohey, 1952).

Frequency of Prothrombin Estimations

After the initial two or three prothrombin estimations necessary in the first four to five days of therapy, it is usually sufficient to carry out prothrombin estimations only twice or, at the most, three times a week. Phenylindanedione is very stable in its action, so that once the individual variation in reaction has been assessed it is not necessary to do daily prothrombin estimations.

It is perhaps advisable to point out here that minor unimportant fluctuations in the prothrombin time, as measured by the one-stage method, are often seen in practice in patients on anticoagulants. Therefore, to avoid unnecessarily frequent alterations in the maintenance doses of phenylindanedione and similar anticoagulants, the method of prothrombin estimation used should allow for a comparatively wide margin in the clotting-time within which the therapeutic control may be regarded as satisfactory. For this reason, phenol-saline thromboplastin is particularly suitable in that the effective therapeutic range of the prothrombin time is two to three times the normal control (or 30 to 45 seconds).

The administration of heparin interferes with the estimation of the prothrombin clotting-times. Therefore, if the patient is having heparin as well as phenylindanedione the sample of blood for prothrombin estimation should be taken at least four hours, and preferably six hours, after the last dose of intravenous heparin.

Summary and Conclusions

Phenylindanedione has been tried as an anticoagulant in 68 patients, mostly cases of coronary thrombosis and deep venous thrombosis. It is a very effective anticoagulant which in its action lies approximately midway between dicoumarol and ethyl biscoumacetate. The dangerous cumulative effect of dicoumarol occurs to a far lesser extent with phenylindanedione, whilst the fact that the metabolism and excretion of phenylindanedione is less rapid than that of ethyl biscoumacetate makes clinical control of anticoagulant therapy with phenylindanedione much easier.

In this series of 68 cases 200 mg. (in two equal divided doses) was given on the first day, followed by 100 mg. on the second day. On this dosage an appreciable fall in the prothrombin level was noticed in 24 hours, and a full therapeutic effect, with a prothrombin concentration in the region of 10-20%, was reached in 36 to 48 hours in nearly all cases.

The further daily maintenance doses of phenylindanedione varied between 50 and 200 mg. In 44 of the 68 cases the maintenance dose lay within the limited range of 75 to 100 mg., and in only five cases did it fall outside the range of 50-150 mg. Phenylindanedione seems to be much more uniform in action, and therefore easier to control, than either dicoumarol or ethyl biscoumacetate.

Important factors in assessing the appropriate daily maintenance dose within the range of 50 to 175 mg. are the weight, age (apparent rather than real), general health, and renal function. The more robust, young, and less acutely ill patients require the largest doses, whilst the frail, elderly, and severely ill cases need the smallest maintenance doses. Any lowering of renal function will materially reduce the amount of phenylindanedione required.

Once the daily maintenance dose has been established, this dose can be continued for a prolonged period without any significant fluctuation in the prothrombin times. (With improvement in a severely ill patient's general condition, a small increase in the daily maintenance dose may sometimes be necessary.) This uniform action of phenylindanedione means that in most cases, once the daily maintenance dose has been established, prothrombin estimations are necessary only twice or, at the most, three times a week. (In patients on prolonged therapy, prothrombin estimations weekly or less often are usually enough.)

No toxic effects from phenylindanedione were encountered in this series. In a small series of seven cases reported previously, the giving of much larger doses than those required to maintain an adequate therapeutic prothrombin level resulted in haemorrhage in one case only and no other toxic reactions. This haemorrhage and the severe prothrombin deficiency seen in the other six cases were quickly controlled within eight to twenty hours by vitamin K₁ given orally.

The total daily dose of phenylindanedione in each case was given in two divided amounts, morning and evening. In most cases it turns the urine a pinkish-orange colour.

I wish to thank Charles E. Frosst and Co. (Canada) for the initial supplies of phenylindanedione ("danilone") and also Evans Medical Supplies Ltd. for additional amounts of the drug ("dindevan"). I also wish to express my gratitude to Dr. E. Lozinski, of Charles E. Frosst and Co., for his help and advice.

REFERENCES

- Bjerkelund, C. J. (1950). *Scand. J. clin. Lab. Invest.*, **2**, 83.
 Blaustein, A. U., Croce, J. J., Alberian, M., and Richey, N. (1950). *Circulation*, **1**, 1195.
 Jaques, L. B., Taylor, E., and Lepp, E. (1949). *Fed. Proc.*, **8**, 81.
 Kabat, H., Stohman, E. F., and Smith, M. I. (1944). *J. Pharmacol.*, **80**, 160.
 Soulier, J. P., and Gueguen, J. (1947). *C.R. Soc. Biol., Paris*, **141**, 1007.
 Toohey, M. (1952). *British Medical Journal*, **2**, 687.

Robert James Graves, who died on March 20, 1853, is best remembered to-day for his accurate account of exophthalmic goitre (1835). Although earlier descriptions of the condition were given by Flajani (1802) and Parry (1815), it is best known in Britain as "Graves's disease." He was one of the founders of the Park Street School of Medicine in Dublin. While physician to the Meath Hospital he introduced Continental methods of clinical teaching with good effect. Graves qualified in 1818 and then studied in London and on the Continent. When he was in Austria his fluency in languages led him to be taken for a German spy and he was imprisoned for ten days. During a journey from Genoa to Sicily the ship in which he was travelling ran into a storm and the crew threatened to abandon ship. Graves seized an axe and smashed the ship's boat; he then assumed command and repaired the pumps with leather from his own boots. Graves contributed many papers to medical literature. His *Clinical Lectures on the Practice of Medicine*, 1848, is considered his best work.

TREATMENT OF NAUSEA AND VOMITING OF PREGNANCY WITH ANTIHISTAMINES

BY

SAMUEL LASK, M.D., M.R.C.O.G.

Obstetrician and Gynaecologist, St. Andrew's Hospital,
London, E.3

During the past few years good results have been reported from the use of antihistamine preparations in nausea and vomiting of pregnancy. Dougray (1949) recorded 94 cases thus treated, with 83% cured, and Carliner *et al.* (1949) reported on 43 patients treated with dimenhydrinate ("dramamine"), with 72% cured. At St. Andrew's Hospital during the past three years a large proportion of patients complaining of nausea and vomiting in pregnancy were freed from these symptoms by taking an antihistamine preparation. So successful was this treatment that it was extended to patients who complained mainly of heartburn, with equally gratifying results. After some months it was decided to make a clinical trial, treating one group of patients with an active antihistamine preparation and another group with an inert preparation.

Method

Although all patients were questioned as a routine on vomiting in pregnancy, only those who specifically complained were treated. Cases were divided into three groups: severe vomiting, in which vomiting occurred at frequent intervals during the day or caused the patient a good deal of distress; occasional vomiting, in which vomiting was not frequent and regular and did not unduly distress the patient; and cases in which heartburn and nausea were the predominant symptoms. No attempt at clinical assessment was made, apart from excluding any obvious non-obstetric cause of vomiting, and the patient's own statement was the guide to the group in which she was placed. As the element of suggestion plays a part in the treatment of these patients, and some patients will respond to any form of therapy, it was decided to include only those who had already received some other form of treatment without improving.

Two antihistamine preparations were used, both in tablet form: mepyramine maleate ("anthisan"), 100 mg., and promethazine-8-chlorotheophyllinate ("avomine"), 25 mg. They appeared to be equally effective. The control tablets contained lactose only, and were identical in size and shape, and almost identical in colour with the active tablets. Patients were divided into two groups of 60; one group was treated with antihistamine tablets and the other group with the inert tablets. The tablets were collected from the hospital dispensary and enough for three days' treatment were given. Patients were instructed to take a tablet at night before retiring. This routine was altered occasionally for those whose symptoms were particularly troublesome at a set time—for example, after the evening meal or after getting into bed at night. These patients were instructed to take the tablet about two hours before the expected time of onset of the symptoms.

Patients were seen five days later at the antenatal clinic. Those who were free from symptoms while taking the tablets were classified as cured; others were classified as improved or unchanged. The short period of three days for treatment was chosen because experience had shown that patients who were going to benefit by the treatment did so almost immediately. There was also the additional factor that by giving a short course of treatment and by