Clinical Use of the Anticoagulant Phenylindanedione

Report of 74 Cases

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Phenylindanedione is an anticoagulant similar in action to the coumarin series of compounds. Like dicumarol, it is effective orally, acts by lowering blood prothrombin content, and its administration is controlled by daily blood prothrombin determinations. A study of the effective dosage, rapidity of action, cumulative effect and hemorrhagic complications produced by this drug shows that it is a practical anticoagulant for clinical use and has certain advantages over dicumarol.

The antiprotease effect of certain indanediones when administered orally to animals was first investigated by Kabat, Stohlman and Smith. Phenylindanedione, an additional derivative, was studied by Meunier, Mentzer and Molho, Soulier and Gueguen, and Jaques, Taylor and Lepp who reported that it is of a low order of toxicity, is a quicker acting prothrombinopenic agent than dicumarol, and that the effect from a single dose is of shorter duration. Bjerkeland demonstrated that phenylindanedione has no effect on the concentration of factor V (Owen) and that vitamin K in large doses intravenously has an antagonistic effect on its prothrombin reducing action. It was first used clinically as an anticoagulant by Soulier and Gueguen and by Blaustein, Croce, Alberian and Richey. The purpose of this paper is to report our experiences in the clinical use of this anticoagulant.

Cases Studied

Seventy-four hospitalized patients were studied. The initial diagnosis in 65 who had thromboembolic episodes before anticoagulant therapy was started was acute coronary thrombosis in 44, thrombophlebitis in 20 and pulmonary embolism in one. Eight patients were given the drug on a prophylactic basis. Four of these had coronary insufficiency and four had congestive heart failure. In addition, a patient with acute pericarditis was treated. Of the cases with thrombophlebitis 17 occurred spontaneously before the patients were admitted to the hospital and four occurred postoperatively. Among the patients with acute myocardial infarction there was one who developed peripheral thrombophlebitis before anticoagulant therapy was started.

Dosage

Initial dosage varied from 75 to 200 mg. given as soon as possible after the diagnosis was made regardless of the time of day. On subsequent days the drug was usually administered twice daily in dosages of 50 mg. Total dosage in 74 patients varied from 350 to 11,040 mg. given over periods of time varying from 5 to 102 days. The average total dose was 2255 mg. and the average duration of treatment was 23 days. The drug was administered orally in tablet form, each tablet containing 50 mg.

Control of Blood Prothrombin

Blood prothrombin determinations were done before anticoagulant therapy was started and daily thereafter until several days after therapy was discontinued or until the blood prothrombin activity had returned to normal. The one stage method of Quick was used, employing a commercial thromboplastin prepared from acetone-dried rabbit brain.
which gave a prothrombin time of 13 seconds in normal patients.∗ Saline suspensions were made freshly each day from dehydrated thromboplastin supplied in ampules. For recalcification 0.02 molar calcium chloride was used. Results were expressed in terms of per cent of normal prothrombin activity. For this thromboplastin a clotting time of 13 seconds represented a prothrombin concentration of 100 per cent and 33 seconds a concentration of 12.5 per cent of normal.

Errors in blood prothrombin determination were kept at a minimum throughout this study by (1) use of thromboplastin with constant activity, (2) daily assays of thromboplastin against normal blood to determine its potency, and (3) experienced technicians (two technicians did over 85 per cent of the determinations). In addition, care was taken not to allow blood drawn for prothrombin assays to stand at room temperature for more than one hour before the determination was made. Quick has emphasized the importance of these factors in securing accurate results.†

Results

Figure 1 illustrates the effect of phenylindanedione on a patient in whom an adequate level of prothrombin depletion was maintained with a dose averaging 85 mg. daily. The rapid fall of blood prothrombin content within the first 24 hours is typical of the action of this drug, as is the return of prothrombin to normal levels within three days after the final dose. Figure 2 illustrates the effect of the drug in a patient in whom control was not quite as satisfactory as the first.

In spite of an attempt to keep blood prothrombin levels between 10 and 30 per cent of normal, there was difficulty in maintaining this deficiency in many instances. In three patients prothrombin activity remained consistently above the therapeutic range in spite of daily doses averaging 109, 118, and 121 mg. respectively, which was greater than the average dose given the remaining patients. These were the only instances of resistance to the drug, and it is probable that satisfactory prothrombin deficiency could have been produced in these patients by increasing the dose. In the remaining 71 patients after the blood prothrombin content had been depressed to the desired level 65 per cent of subsequent daily determinations fell within the 10 to 30 per cent range until the drug was discontinued. In three patients the prothrombin was below 10 per cent of normal activity for at least two consecutive days, and in one instance it was thought necessary to correct the deficiency by the administration of whole blood and vitamin K intravenously. In 31 patients the prothrombin activity rose to above 30 per cent for at least three consecutive days, and in 29 patients there was an escape to over 50 per cent of normal on at least one occasion.

Administration of the drug to these patients was in most cases done by resident physicians who determined the dose each day from the patient’s prothrombin determination of 9 a.m. In general with more experience better control of prothrombin levels is obtained, and it is probable that the control in these patients is

∗ Manufactured by Cappel Laboratories, Wayne, Pa.

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similar to what would be obtained by most physicians interested in using this anticoagulant.

The average daily dose required for maintenance of prothrombin deficiency was increased by dividing the dose, 79 mg. daily for 22 patients who received the drug once daily and 102 mg. for 43 patients who received it twice daily.

Age did not seem to affect the dose requirement appreciably. The amount required to maintain satisfactory prothrombin depletion in patients who received the drug twice daily averaged 103 mg. daily for 10 patients under 50 years of age, 96 mg. for 21 patients 50 to 60 years of age and, 100 mg. for 19 patients over 60 years of age.

One patient with acute myocardial infarction had a fresh infarction proved at necropsy while on anticoagulant therapy. A second patient had multiple pulmonary infarcts verified at necropsy, some of which may have occurred during the time of therapeutic prothrombin deficiency. No other episodes of fresh thrombosis or embolism were observed in any patient while under therapy with phenylindanedione.

The mortality in 44 patients with myocardial infarction was 13.3 per cent. Although this mortality compares favorably with reported series treated with dicumarol\textsuperscript{9, 12, 13} the number of cases is not large enough to be significant. It is planned to make these patients the subject of a separate report when a sufficient number of cases is added.

Toxic Manifestations

Soulier and Gueguen\textsuperscript{15} using doses three to four times as large as ours reported mild reactions consisting of polyuria, polydipsia and tachycardia in some patients. However, in our series no toxic effects other than hemorrhagic phenomena were observed.

Gross hematuria occurred in one patient whose prothrombin concentration had dropped to less than 6 per cent of normal. It was not definite that the hematuria was related to the anticoagulant because an indwelling catheter was in place; however, the hematuria subsided when the prothrombin was allowed to resume a higher level.

Routine urinalyses were done during the course of therapy in 34 patients at approximately weekly intervals. Transient microhematuria occurred in two (5.9 per cent) when prothrombin concentrations were 8 per cent and 15 per cent respectively. In both patients, the hematuria promptly cleared when the anticoagulant was omitted and the prothrombin concentrations were allowed to resume slightly higher levels.

A hemorrhage of about 250 cc. occurred from a paracentesis site in a patient with thrombophlebitis and hepatic insufficiency at a time when his prothrombin activity was 5 per cent. This hemorrhage was not severe, and it was not definitely attributable to the anticoagulant.

Petechiae involving both lower extremities occurred in one patient on the third day of therapy when the prothrombin was 15 per cent of normal activity. These gradually cleared after the prothrombin was allowed to return to 36 per cent but reappeared on one other occasion during the ensuing 35 days of anticoagulant therapy. Both episodes occurred during quinidine administration.

Prolonged Therapy

Ten patients received the drug for periods of time varying from 33 to 102 days (average 49 days). Total doses received by this group varied from 4125 mg. to 11,040 mg. (average 5687 mg.) None developed an altered tolerance for the drug, and no toxic effects were apparent in these patients.

One of these patients died at home six days after his discharge from the hospital and seven days after his last dose of phenylindanedione. Total dose for this patient had been 5125 mg. during a 41 day period. Necropsy showed that the cause of death was a fresh myocardial infarction. Gross and microscopic examination of the heart, liver, kidneys, spleen, adrenals, gastrointestinal tract and pancreas revealed no toxic effects attributable to the anticoagulant.

Discussion

Interest in phenylindanedione and other dicumarol substitutes has been stimulated by
reports emphasizing that the use of dicumarol has led to serious hemorrhagic complications in some patients. Major hemorrhage occurred in 1.9 per cent of 9,609 patients given dicumarol according to a review of the literature,\(^1\) and in 2 per cent of 15,500 patients treated with dicumarol and heparin by 136 physicians according to a questionnaire.\(^1\) Wright and Rothman\(^7\) have recently reported four cases of fatal hemorrhage following dicumarol administration and summarized 32 other cases from the literature.

It is known that phenylindanedione produces a hemorrhagic diathesis in animals similar to dicumarol if its administration is continued.\(^6\) Whether it will prove to be a safer anticoagulant in humans remains to be seen. No serious hemorrhagic complications have so far been observed in approximately 200 cases previously reported in the literature.\(^5\), \(^4\), \(^10\) The fact that no serious hemorrhages occurred in our patients may be attributable in part to our previous experience with anticoagulants especially dicumarol.

Phenylindanedione has two definite advantages over dicumarol, more rapid action and less cumulative effect. Therapeutic levels of prothrombin deficiency are usually achieved 18 to 36 hours after the initial dose of phenylindanedione, compared with 48 to 72 hours with dicumarol. For rapid anticoagulant effect one must use heparin in conjunction with these drugs. This may be necessary for the first two or three days of anticoagulant therapy with dicumarol but is rarely necessary for more than one day with phenylindanedione.

The effect of phenylindanedione on the prothrombin time usually persists for two to four days after the final dose, as compared to three to seven days after the final dose of dicumarol. This more transient effect of phenylindanedione is particularly advantageous if hemorrhagic complications or other reasons for interrupting anticoagulant therapy occur.

**Conclusions**

1. Phenylindanedione was used to maintain prothrombin deficiency in 74 patients with thromboembolic disease for periods varying from 5 to 105 days.

2. The recommended initial dose is 150 to 200 mg. A maintenance dose of 50 mg. twice daily will usually maintain blood prothrombin levels between 10 and 30 per cent of normal activity.

3. The desired prothrombin deficiency was usually present 24 hours after the initial dose, and, after the last dose, prothrombin concentration returned to normal in 48 to 96 hours.

4. Resistant patients are infrequent and no patients developed an altered tolerance for the drug while undergoing therapy.

5. Hemorrhagic complications (including microhematuria) occurred in five patients (6.8 per cent) but none were of major significance.

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Circulation. 1952;6:515-519
doi: 10.1161/01.CIR.6.4.515

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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