CHLORPHENINDIONE—A NEW LONG-ACTING ORAL ANTICOAGULANT

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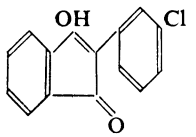
Preliminary reports have shown that chlorphenindione is a long-acting oral anticoagulant (Lund, 1957; Pugatsch, 1960). The chemical structure of the drug, which is one of the indanedione group, is as follows:



2-(4′-chlorphenyl)-indanedione-(1,3)

The aim of the present investigation was to assess the value of this new agent in the short-term treatment of thromboembolic disorders in comparison with a well-established drug, nicoumalone ("sinthrome"). It is marketed on the Continent and has been recommended for routine short-term and long-term therapy.

Method of Study

The drugs were compared in two consecutive periods of time in unselected groups of patients in the anticoagulant service at Withington Hospital. Patients whose individual treatment was of less than 10 days' duration were later excluded from the trial.

The laboratory control was based on the Quick prothrombin time. Prothrombin activity was determined in all cases before treatment was begun and then daily until the prothrombin level was reduced to below 30%. Further estimations were performed as required in each individual case once the patient was "stabilized." The number of days required to "stabilize" the prothrombin time was noted in every case. This was arbitrarily determined as the number of days required to achieve a level within the therapeutic range that was maintained for three consecutive tests. It was thought possible that the use of a drug with a prolonged action might reduce the number of tests required to control in-patient therapy. The total number of tests was correlated with the number of days on treatment for the two groups. No conscious effort was made to reduce the number of tests performed during treatment with the two drugs, the number being governed entirely by the response of the patient.

The number of days that the prothrombin activity was maintained within the limits of the 10–40% range was calculated for both drugs in order to assess their stability of action. Patients with myocardial infarction constituted the largest group treated with anticoagulants (Table I). Speed of action is an important consideration in this condition, which has a high mortality in the first few days. The number of days required to depress the prothrombin activity to less than 30% was calculated for both drugs.

Some patients on oral anticoagulants are refractory to treatment. The term "drug resistance" is often used in this sense, although it has not been precisely defined. Here we have taken as its definition the need to administer a dose for maintenance therapy which approximates to or exceeds the initial loading dose. In the case of both drugs the loading dose was 12 mg. on the first day and 8 mg. on the second, provided the prothrombin activity was above 40% at this stage. Where initial results were less than 100%, or there was a response to treatment considered to be excessive after 24 hours, appropriately smaller doses were administered. Some cases were very sensitive to the action of the anticoagulants, and those requiring 1 mg. a day or less as a maintenance dose were recorded as being "sensitive" cases in both series.

TABLE I.—*Number of Cases Treated*

	Nicoumalone	Chlorphenindione
Myocardial infarction	30	35
Thrombophlebitis	3	5
Cerebral embolism	2	2
Pulmonary ,,	1	3
Angina	—	2
Aortic embolus	1	—
Circulation defect	1	—
Total	38	47
Average age	56·7 years	60·5 years

The number of side-effects was recorded for each group of patients. This was felt to be important because chlorphenindione belongs to the same type of drugs as phenindione ("dindevan"), which has well-known toxic effects. Mortality and thromboembolic complications were observed in each group. This is by no means a true indication of the effectiveness of treatment with the two drugs as this was a selected trial, patients receiving less than 10 days' treatment being excluded. The inclusion of these figures, however, gives an impression of the effectiveness of treatment in the cases considered.

The same batch of thromboplastin was used in the Quick test throughout the investigation. This gave similar results to other batches of acetone-dried human brain thromboplastin which had been in use for several years in this laboratory. The lower limit of the therapeutic range which has been found by experience to be associated with a negligible risk of haemorrhage is 10%. The upper limit of therapeutic activity appears to be in the region of 40%, which is one and a half times the control time. This upper limit of 40% corresponds to readings between 15 and 25% from simultaneous tests with Owren's (1959) thrombotest (Poller, 1962).

Heparin (10,000 units six-hourly) was administered intravenously to all patients with myocardial infarction and pulmonary embolism; it was given for 36–48 hours in these cases. Blood was taken for the prothrombin estimation on the second day at the period of minimum heparin activity—that is, six hours after the intravenous dose.

Technique: Quick (1935) One-stage Prothrombin Time Modified

Venous blood (4.5 ml.) was collected into a bijou bottle containing 0.5 ml. of 3.8% trisodium citrate. The thromboplastin reagent was prepared from acetone-dried human brain. A phenol–saline extract was prepared (Powell, 1957) which gave normal prothrombin times of 11–13 seconds. A dilution curve was obtained by the saline dilution of normal plasma; the results from six normal subjects were averaged.

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The test proper consisted in pipetting 0.1 ml. of thromboplastin reagent into a 10 by 70-mm. test-tube in a water-bath at 37° C. and allowing the reagent to warm up for at least five minutes. The reagent could be incubated up to two hours without deterioration. The test plasma (0.1 ml.) was then added, and the contents of the tube were mixed gently. Within 20 seconds of mixing, 0.1 ml. of the warm M/40 calcium chloride was added, a stopwatch being started simultaneously. The tube was tilted to and fro until a clot was seen to form. The results were the average of three tests on each specimen. All tests were performed within an hour of collecting the specimen of venous blood.

Results

On an average it required 1.94 days to reduce the prothrombin activity to less than 30% in the nicoumalone group and 2.84 days in the chlorphenindione group. The time required to stabilize the prothrombin level was also noted for each group. This was 3.6 days for nicoumalone and 3.2 days for chlorphenindione. Although slower in action, the chlorphenindione achieved "stability" more rapidly. Once a therapeutic level had been reached, 87.7% of results were within the therapeutic range with nicoumalone and 91.3% with chlorphenindione. In Table II the difference between the results achieved

TABLE II.—*Results*

	Nicoumalone	Chlorphenindione
No. of cases	38	47
,, ,, treatment days	1,143	1,179
,, ,, tests	559	617
Total No. in 10–40% P.T.I. range	430 (76·9%)	477 (77·3%)
Treatment days per test	2·05	1·91

with the drugs arises from the inclusion of all estimations, including those before treatment was begun. Slightly better control appeared to result from nicoumalone therapy. This is due to the inclusion of results after 24 hours, when chlorphenindione had not yet achieved its full activity.

There were three "resistant" cases in the nicoumalone series and four in the chlorphenindione. There were two "sensitive" cases in the nicoumalone series and four in the chlorphenindione. Three cases were listed as difficult to "stabilize" and all occurred in the nicoumalone group. One minor haemorrhage (subconjunctival) occurred. This was in the nicoumalone group. No other haemorrhage was noted in either series. Two deaths occurred in each series. There were no thromboembolic complications in either series.

TABLE III.—*"Escapes" on Therapy*

	Nicoumalone	Chlorphenindione
Escapes above 40%	43 (7·7%)	34 (5·5%)
,, below 10%	17 (3·0%)	13 (2·1%)

The loading dose required within the first 48 hours ranged from 12 to 32 mg. with nicoumalone and 4 to 24 mg. with chlorphenindione. The range of maintenance requirements in the nicoumalone series was 1–20 mg.; in the chlorphenindione series it was from <1 to 16 mg. daily.

Discussion

There are many anticoagulant drugs now available for oral administration. All have different dosage schedules, and confusion may arise from the multiplicity of names. To justify the introduction of a new agent it must be shown to have appreciable advantages. We have assessed the points which we consider to be important in the appraisal of a new anticoagulant agent.

The degree of control achieved with chlorphenindione appears reasonably good but is not convincingly better than with the established drug, nicoumalone. The improvement in maintenance control with chlorphenindione was probably more than offset by the slow speed of action in patients with a considerable potential mortality in the first 48 hours after a thrombotic episode. It took nearly 48 hours to achieve a therapeutic effect with nicoumalone and nearly three days with chlorphenindione. It was therefore apparent that in the chlorphenindione series heparin therapy was not sufficiently prolonged. Consequently it is desirable that heparin should be administered for at least 72 hours with this drug. The use of chlorphenindione does not appear to reduce the number of tests required to control short-term anticoagulant therapy in hospitals.

Although reduction in the number of tests was not the primary aim of the investigation, this would have been a good point in favour of the new agent if a convincing difference had been achieved. "Escapes" above 40% are somewhat higher in the nicoumalone group. This was usually due to a "rebound" effect noted after recovery from the loading dose of nicoumalone. "Rebound" effect was due to the difficulty in predicting the appropriate maintenance dose on the third day of therapy when the loading dose was still taking effect. With a relatively quick-acting drug such as nicoumalone rapid excretion occurs, and if the dose on the third day, which errs on the side of safety, is insufficient the prothrombin activity rises much quicker than with the relatively slow-acting chlorphenindione. This will be seen in the figures for the time required to "stabilize" the patients in the therapeutic range, which were slightly higher with nicoumalone. The number of cases requiring very small doses was similar in the two groups. Thromboembolic complications and mortality show no appreciable difference in the two groups, although not much significance can be placed on such an observation in a selected trial of this sort.

Summary

A clinical trial of short-term anticoagulant therapy with chlorphenindione, a new long-acting agent, has been carried out. The results in 47 patients have been contrasted with those achieved with nicoumalone, an established drug, in 38 patients. Slightly better control was achieved with the new long-acting drug, but this was offset by its slower speed of action. The slow initial action can be overcome by prolonging heparin therapy for 72 hours.

Gratitude is expressed to Dr. P. D. Fowler and to Geigy Pharmaceutical Company Ltd., Wythenshawe, Manchester, for supplying chlorphenindione (G. 25,766).

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