Clinical Trial

A TRIAL OF CLORINDIONE—A LONG ACTING ORAL ANTICOAGULANT

D. A. KING, M.B., M.R.C.P.

Medical Registrar, Harrogate General Hospital.

IT HAS been shown that clorindione (2-(4'-chlor-phenyl)-indanedione-(1.3)) is a long acting anticoagulant. Lund (1957), Strobel (1962) and Poller and O'Brien (1962) demonstrated that it required 2-3 days for the prothrombin activity to be depressed to within the therapeutically effective range. It was shown by Strobel that the prothrombin activity increases to above the range after 4 days and becomes normal 6 days after a single dose of clorindione. He also gives details of the physical and chemical properties of the drug.

The purpose of this investigation was to assess the value of this anticoagulant in both inpatient and outpatient treatment of thrombo-embolic diseases.

Methods

The drug was administered to 32 patients. From the start of the trial it was given to all patients considered to need anticoagulant treatment unless at the time of admission they were being treated with another anticoagulant or unless there were the usual contradictions such as indigestion. No attempt was made to compare the drug with other anticoagulants.

32 patients were treated in hospital, 22 of whom were males. The ages ranged from 33 to 75 years, the average age being the same for both sexes. 14 were later treated as outpatients and as would be expected they represent the patients who continued to take the anticoagulant after discharge from the hospital. Of the remaining 18 patients, two died of cardiac failure after 11 and 25 days respectively and the condition of the others was not thought sufficiently severe to warrant anticoagulant treatment after discharge. The following table shows the clinical diagnoses and their distribution between the sexes.

Of the patients with pulmonary infarction 5 were secondary to phlebothrombosis of the leg and of the remaining 3 there was no obvious source of a possible embolus. The patient with cerebral embolism suffered from mitral stenosis and auricular fibrillation

and had had a mitral valvotomy performed 8 months previously.

The prothrombin time was not estimated routinely on the day of admission but was measured from the 4th to 8th days inclusive of treatment. Further estimations were done once to twice weekly. The total number of tests performed and the number within the therapeutic range were recorded. The pathological department of the hospital performs a modified form of the Quick method using Simplastin (Messrs. William R. Warner and Co. Ltd.), which already contains calcium and sodium chloride and to 0.1 ml. of Simplastin is added 0.05 ml. of plasma. We have found from our experience with clorindione and other anticoagulants that depression of the prothrombin time below 2½ times the normal control is attended with the risk of haemorrhage and we therefore work to a therapeutic range of prothrombin times of 2.5 and 1.6 times the control time. This corresponds to a range of prothrombin activity of 12% to 20% according to the activity curves prepared by the manufacturers of Simplastin. With the outpatients we modified the range to 2.3 to 1.7 times the control, that is a prothrombin activity of 15% to 25% to allow for greater safety.

The doses of clorindione used in this trial were 12 mg. on the first, 8 mg. on the second and 4 mg. on the third day. Each tablet contains 4 mg. of clorindione and is easily halved. Because of the delay before the drug becomes effective heparin 10,000 i.u. was given by intramuscular injection on admission and then 5,000 i.u. every 6 hours for 3 days. The drug was given at 24 hourly intervals.

The duration of treatment was noted and patients whose treatment lasted less than 5 days were excluded from the analysis. There were 2 such patients, one of whom died on the third and the other on the fourth day from cardiac failure following myocardial infarction.

The complications of the drug were recorded and the serum glutamic oxalacetic and glutamic pyruvic transaminases were estimated on the day of admission, 3 days and weekly thereafter while the patient was in hospital.

TABLE 1

		Myocardial Infarction	Phlebothrombosis	Pulmonary Infarction	Cerebral Embolism	Total
Inpatients	M	13	3	6	—	22
	F	6	1	2	1	10
Outpatients	M	9	2	1	—	12
	F	1	—	—	1	2

Results

Of the 32 inpatients 7 were not within the therapeutic range by the fourth day and 4 by the sixth day but all were within the range by the eighth day. 4 were below the lower level of the range on the fourth day. Of those patients whose prothrombin time was greater than 1.6 times that of the control on the fourth day (prothrombin activity of less than 20 per cent) of whom there were 25, 2 lapsed below that figure within the following 4 days but returned to within the range by the eighth day.

After the first 8 days a total of 120 tests were performed on the inpatients. 31 were above the upper limit of the range and of those, 18 were on the 7 patients whose prothrombin time was not satisfactory by the fourth day.

In the outpatient group 90 prothrombin time estimations were performed and of those 77 were within the therapeutic range. 4 were below the lower limit of the range. Estimations were done at intervals of from 2 to 4 weeks.

The duration of treatment varied from 5 to 47 days in the inpatient group and there were 646 treatment days. In the outpatient group the duration of treatment varied from 11 days to 13 months and there were 1,980 treatment days. 4 patients were treated for over 10 months as outpatients.

The maintenance dose varied. Of the inpatients 8 required 2-4 mg. per day, two 2 mg./day, ten 4 mg./day, eight 4-6 mg./day and 4 required 6-8 mg./day. The outpatients requirements on the whole were similar to those when the patients were in hospital. There was no correlation between age or sex and the dosage but the maintenance doses tended to be higher in those patients whose prothrombin time was not within the therapeutic range by the fourth day of treatment. Table 2 gives a brief review of the results.

Complications

No sensitivity reactions developed. The serum transaminase levels were all within normal limits except in the early estimations from those inpatients with myocardial infarction and in some with pulmonary infarction. In these patients the levels were normal from the third estimation onwards. Bleeding occurred in 5 of the patients i.e. 15.6%. 3 developed haematuria and 1 of these had a urinary infection and an indwelling catheter. The fourth developed ecchymoses. In

these 4 cases the drug was stopped for 2 days by which time the bleeding had ceased and the prothrombin time had fallen to less than 1.7 times the normal control. The fifth case had a haematemesis and it was only then that she admitted to previous symptoms suggestive of peptic ulceration. The drug was withdrawn. In none of these cases was bleeding sufficiently severe to warrant treatment with Vitamin K. One inpatient suffering from myocardial infarction and cardiac failure who was difficult at first to stabilise, developed phlebothrombosis of the leg on the seventh day of treatment but this settled with continued treatment.

In the outpatient group one developed haematuria and another had ecchymoses. Another had a recurrence of myocardial infarction but her prothrombin time was less than 1.5 times normal 10 days before the incident. She made a good recovery on continuation of the drug in hospital. Among the inpatients there were 2 deaths from cardiac failure secondary to myocardial infarction.

Discussion

Poller and O'Brien's recommendation that heparin be used during the first 3 days was followed. This we found to be the only disadvantage of using clorindione. The drug was found to be effective in prolonging the prothrombin time to a therapeutic level on the fourth day of treatment in 78% of the patients and of these only 8% lapsed during the next 4 days. Thus induction was smooth and rebound phenomena rare. We confirmed the smoothness of the prothrombin time or activity curves which previous assessors found on maintenance doses both as in- and outpatients. Large swings were rare even among the outpatients where testing averaged once in 22 days. In this group, 14% of the tests were above the upper limit of the therapeutic range. Of the inpatient tests 79% were within the range. No resistant or unduly sensitive cases were encountered and the dosage levels were reasonable.

The only complications of the drug were haemorrhagic episodes in 15.6% of inpatients and 14.3% of outpatients. These figures are comparable with those of the other anticoagulants using a similar therapeutic range (Sevitt and Innes 1964).

Summary and Conclusions

Clorindione, one of the newer anticoagulants, was tried in 32 patients in hospital and continued

TABLE 2

	No. of patients	No. of tests	No. of tests within therapeutic range	Complications	Dosage range (in mg.)	Duration of treatment (in days)	Average daily dose	Treatment days/test
Inpatients	32	280	222	5	2-8	646	4.3	2.9
Outpatients	14	90	77	2	2-8	1980	4.7	22

in 14 as outpatients for periods of from 5 to 47 days in the former group and from 11 days to 13 months in the latter. The drug has a slow speed of action and herapin was administered during the first 72 hours. Good smooth control was obtained in both groups and haemorrhagic complications were relatively few. This anticoagulant is a useful and reliable one and the ease of control adequately compensates for the initial slowness of action.

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