gated in the unconscious, curarized subject. The Schafer and Holger Nielsen methods have been compared with mouth-to-mouth ventilation and a simple bellows resuscitator.

Manual methods have the advantage of requiring no apparatus, but they do require space. They are not so efficient for the oxygenation of the subject and may be relatively ineffective in the presence of bronchoconstriction.

Intermittent positive-pressure methods require apparatus, but are superior in terms of ventilation and oxygenation. The bellows resuscitator, a simple, compact apparatus, was still more efficient than the mouth-to-mouth apparatus.

The bellows resuscitator used in this investigation was designed and supplied by the Chemical Defence Experimental Establishment, Porton, Salisbury.

REFERENCES

- Beecher, H. K., and Murphy, A. J. (1950). *J. thorac. Surg.*, **19**, 50.
Lucas, B. G. B., and Milne, E. H. (1955). *Thorax*, **10**, 354.
Mushin, W. W., and Morton, H. J. V. (1958). *Brit. med. J.*, **1**, 215.
Nielsen, H. (1932). *Ugeskr. Læg.*, **94**, 1201.
Schafer, E. A. (1904). *Med.-chir. Trans.*, **87**, 609.

CLINICAL EVALUATION OF "MIRADON"

BY

GAVIN KELLAWAY,* M.B., M.R.C.P., M.R.C.P.Ed.
*Registrar, Department of Cardiology,
Royal Infirmary, Edinburgh*

The value of anticoagulants in the treatment of certain thrombo-embolic conditions is now well established. Since the introduction of dicoumarol about 17 years ago (Butt *et al.*, 1941; Wright and Prandoni, 1942; Overman *et al.*, 1942), a number of hydroxycoumarin and indanedione derivatives, causing depression of the prothrombin activity of blood, have become available for use as anticoagulants. In addition to dicoumarol, these include ethyl biscoumacetate ("tromexan") (Tulloch and Gilchrist, 1951; Burke and Wright, 1951), phenindione ("dindevan") (Jaques *et al.*, 1950), phenylpropyl-hydroxycoumarin ("marcoumar") (Bourgain *et al.*, 1954), cyclocoumarol ("cumopyran") (Hanson *et al.*, 1951), and, more recently, warfarin (Clatanoff *et al.*, 1954) and nicoumalone ("sintrom") (Weiner *et al.*, 1956). They all suffer the disadvantage of being potentially dangerous and require frequent estimations of the prothrombin time for their control. As yet, however, they remain the best available drugs for treatment where prolongation of the prothrombin time is desired.

The purpose of this paper is to report the clinical trial of a new anticoagulant, 2-*p*-anisyl indanedione—1,3(C₁₆H₁₂O₃), called "miradon" (anisindione). It appears to be more rapidly effective than and just as readily controlled as any anticoagulant in current use.

Material and Methods

Miradon has previously been tested in animals (P. L. Perlman and P. C. Giordano, unpublished work) without evidence of toxicity. It has the following chemical structure.

*Now at Green Lane Hospital, Auckland, New Zealand.

Like phenindione, to which it is chemically related, miradon exercises its therapeutic action by depression of the prothrombin activity of the blood. In the presence of alkaline urine an orange colour is often detected, the result of katabolites of miradon.

Miradon was supplied in 50-mg. tablets for oral use, and the clinical trial was divided into three parts.

Part I.—A loading dose of 300 mg. was given to 12 healthy subjects, and the onset, rate, degree, and duration of prothrombin activity depression were recorded. None of these patients required anticoagulant therapy and all were free from known renal or hepatic disease. Estimations of the prothrombin time were performed according to the Quick one-stage method (Quick, 1942), using a phenol-saline preparation from human brain as a source of thromboplastin. Each batch of thromboplastin was diluted to obtain prothrombin % activation curves, and the results presented here are given as prothrombin % activity. The normal control using this method varied from 11 to 14 seconds. Prothrombin activity of 10 to 20% was regarded as a satisfactory therapeutic range; this corresponds approximately to two to three times the normal plasma prothrombin time. Prothrombin activation curves were obtained for each patient.

Part II.—This constituted a therapeutic trial in 25 patients in whom anticoagulant therapy was thought to be necessary. These patients comprised 25 consecutive admissions who would otherwise have received therapy with another anticoagulant. Of these patients, 20 were suffering from a recent myocardial infarct, two from acute coronary insufficiency of increasing severity, two from deep venous thromboses of the legs (one of these had also suffered a pulmonary infarct), and one patient was given anticoagulant therapy while he received treatment to convert auricular fibrillation to normal rhythm. The aim in treatment was to maintain the prothrombin activity between 10 and 20%, and the dose for patients was ordered each day by the one observer. Estimations of the prothrombin time were performed before treatment began, 24 hours later, and thereafter daily between 9 and 10 a.m. for the first two weeks and for two out of every three days thereafter until treatment had been completed. During the course of this trial, random 24-hour periods were studied more closely to observe variations in prothrombin activity. The initial dose was 300 mg., except in three patients suffering from myocardial infarction in whom cardiac failure was present. (In these patients the initial dose given was 250 mg.) After 24 hours a further dose of 100 mg. was given, and thereafter the single daily dose depended upon the prothrombin times.

Part III.—The effect of oral vitamin K₁ on the prothrombin time was observed in a number of patients in whom "therapeutic levels" had been maintained for at least three days. The effect of vitamin K₁ was assessed further by the simultaneous oral administration of 20 mg. together with 300 mg. of miradon.

Results

Part I

In 11 of the 12 subjects given 300 mg. of miradon orally there was an effect upon the prothrombin time within six

TABLE I.—Effect of a Loading Dose of 300 mg. of Miradon

Subject	Duration of Effect (Hours)	Prothrombin % Activity at Start	Prothrombin Activity Less than 25% (Hours)	Maximum Effect	
				Prothrombin %	Time (Hours)
1	6-64	40	24-52	12	34
2	8-106	50	26-58	17	50
3	4-58	100	—	30	26
4	6-58	60	26-38	17	34
5	6-96	40	20-52	14	28
6	6-72	47	26-38	17	34
7	6-58	40	20-40	13	34
8	6-96	100	26-58	22	28
9	6-64	80	22-40	13	28
10	6-60	80	22-46	16	28
11	6-58	80	—	30	30
12	6-52	100	—	28	26

hours (Table I). In one subject no effect was evident before eight hours, while in another prolongation of the prothrombin time occurred within four hours. After a sharp fall in prothrombin activity to the region of 50 to 70% of the original level there was a slower decrease over the ensuing 4 to 10 hours, followed again by a steeper fall to the maximum effect, which was present between 20 and 50 hours (average 34 hours). The average duration of effect was from 6 to 70 hours, with an overall range of 4 to 106 hours. Seven of the 12 subjects were within the average range. Typical prothrombin activation curves are illustrated in the Chart. The trial dose was sufficient to produce the desired therapeutic level of 10 to 20% prothrombin activity in 8 of the 12 subjects, while in the other 4 the lowest level produced was between 21 and 30%.

Effect of 300 mg. of miradon upon prothrombin activity in four subjects.

By way of comparison, 12 similar subjects were given 200 mg. of phenindione. The average duration of effect was from 10 to 60 hours, with an overall range of 8 to 100 hours. Eight of the 12 subjects were within the average range, while the average maximum effect occurred at 30 hours. In these subjects the lowest level of prothrombin activity produced by this loading dose varied from 16 to 49%. This may be compared with the range of 12 to 30% observed above with miradon.

Part II

A satisfactory therapeutic effect upon the prothrombin activity was obtained in all patients (Table II). The prothrombin activity was within the therapeutic range (10–20%) within 24 hours of the initial dose in 16 of the 25 patients. When these results are combined with those obtained in

TABLE II.—Response in Prothrombin Activity 24 Hours After the Initial Loading Dose of 300 mg. of Miradon and the Percentage of Subsequent Prothrombin Estimations Within Therapeutic Levels

Name	Age	Prothrombin Activity at 24 Hours	Days Treated	% Results with Prothrombin Activity 10–20%
H.R.	49	28	28	79
A.J.	80	16	25	88
J.M.	71	17	26	90
T.U.	67	21	28	78
J.H.	75	21	26	80
J.McF.	37	16	21	81 (Died)
G.C.	49	20	26	90
F.W.	51	15	26	72
E.McA.	52	26	26	90
H.K.	65	23	26	87
R.C.	65	23	27	83
J.R.	66	13	26	94
W.A.	56	20	27	95
E.McA.	55	16	5	67 (Died)
A.L.	58	16	28	81
J.S.	56	17	26	84
M.W.	42	17	26	95
I.B.	58	18	36	75
A.S.	56	16	26	94
J.McC.	56	19	26	94
A.H.	45	22	12	86
I.G.	77	22	27	100
J.G.	66	20	27	94
J.McK.	72	19	27	87
M.S.	56	24	26	87

Part I, 56% of the 37 subjects had prothrombin activity within the therapeutic range at 24 hours, and a further 30% had a prothrombin activity between 21 and 24% (Table III). After the first 24 hours, 86% of the 472 estimations of the prothrombin time performed were within the therapeutic range, 7% were narrowly outside this range (21–24%), and only 2% occurred in the 25 to 30% group. There were no estimations showing less satisfactory control than this, and, of the 5% recorded as having a prothrombin activity of less than 10%, the most prolonged prothrombin time was one of 62 seconds at a time when the control was 14 seconds.

The uniformity of prothrombin activity as a result of single daily doses of miradon was demonstrated by closer observation of random 24-hour periods in eight patients (Table IV). Little significant variation was evident throughout these periods.

TABLE III.—Effect of 300 mg. of Miradon on the Prothrombin Activity at 24 Hours

Prothrombin Activity at 24 Hours	No. of Patients	% of Total
Less than 10%	0	0
10–20%	21	56
21–24%	11	30
25–30%	5	14

TABLE IV.—Uniformity of Prothrombin Levels Throughout Random 24-Hour Periods in Eight Patients Treated with Miradon

Subject	0 Hours	8 Hours	12 Hours	20 Hours	24 Hours
1	13	11	10	11	11
2	11	13	11	10	11
3	17	18	19	20	19
4	14	18	18	15	15
5	12	12	18	14	15
6	12	11	12	10	12
7	12	13	14	12	12
8	12	15	15	11	13

Once therapeutic levels had been obtained, the daily maintenance dose varied from 25 to 350 mg. In two-thirds of the patients the variation between maximum and minimum doses required to maintain therapeutic levels was 100 mg. or less. The average maintenance dose was 100 mg. a day. One instance of mild resistance was noted in a patient in whom there was an initial satisfactory response to 300 mg. and subsequent doses of 100 mg. a day. It became necessary to increase the dose by stages to 350 mg. a day to maintain control. This patient was later treated with phenindione, to which he showed a more marked degree of resistance, and doses of 550 mg. daily were necessary to produce therapeutic levels. In the remaining 24 patients the maintenance dose varied from 25 to 250 mg.

The time taken for the prothrombin level to return to normal on discontinuation of therapy was observed in 10 of the 25 patients. In all instances at 24 hours the prothrombin activity was within 3% of the previous reading. At 32 hours the prothrombin time of two patients had returned to normal, and by 72 hours normal prothrombin times were recorded in all 10 patients.

Throughout these trials toxic side-effects were not observed, there were no haemorrhagic episodes, haematuria was not encountered, and in those patients in whom liver-function tests were performed prior to treatment no change was observed after therapy.

Part III

Vitamin K₁ given orally in doses of 20 mg. produced an appreciable response on the prothrombin time within four to six hours, and in six subjects normal levels were produced within 10 to 12 hours. Vitamin K₁ in 20-mg. doses given intravenously resulted in a fall to normal levels within four hours. A similar oral dose of vitamin K₁ given together with the loading dose of miradon resulted in an absence of subsequent hypoprothrombinaemia. Miradon was thus satisfactorily antagonized by vitamin K₁.

Discussion

In general, anticoagulants may be used therapeutically either in short courses of 14 to 28 days, as in deep venous thrombosis and recent myocardial infarction, or for more prolonged therapy in the prophylactic treatment of coronary thrombosis or embolic phenomena.

Ideally, anticoagulants must be free from toxic side-effects. In addition they should be readily metabolized and excreted. They should maintain the prothrombin time within therapeutic levels and without wide variations. In the event of spontaneous haemorrhage a rapid reversal of anticoagulant action with vitamin K₁ is necessary. In these days of increasing Health Service costs they should also be reasonably priced. In short-term therapy the requirements are more exacting, and, in addition to the "ideals" already mentioned, a rapid, uniform, and predictable response to a standard dose is highly desirable. Equally important is the uniformity of prothrombin time response from day to day, so that any doctor unaccustomed to the daily regulation of anticoagulant dosage may not find control difficult.

The relative merits of the various hydroxycoumarin and indanedione anticoagulants have been fully discussed by previous workers (Brodie *et al.*, 1952; Scarrone *et al.*, 1952; Coon *et al.*, 1953; Weiner *et al.*, 1956; Prior, 1957). For long-term therapy the rapid production of therapeutic levels and early uniformity of response are not essential. Once over the initial difficulties of stabilization, most anticoagulants prove satisfactory for this form of treatment. The longer-acting anticoagulants (phenylpropylhydroxycoumarin, warfarin, and cyclocoumarol) are suitable for prolonged prophylactic therapy, but the time taken to acquire therapeutic levels and the delay in returning to these levels when control is unsatisfactory make them less desirable than the shorter-acting anticoagulants ethyl biscoumacetate and phenindione for short-term therapy.

Although ethyl biscoumacetate is very rapidly absorbed the considerable variation in dose required to produce therapeutic levels tends to offset this advantage (Weiner *et al.*, 1953; Vander Veer *et al.*, 1953). Coon *et al.* (1953) thus found that a greater percentage of patients treated with phenindione were within the therapeutic range at 24 hours than with ethyl biscoumacetate, despite its slower absorption. They found also that there was less difficulty in maintaining constant levels with phenindione, and these factors, coupled with the excessive cost of ethyl biscoumacetate, have led to the more general use of phenindione. As phenindione is, in our experience, the most satisfactory anticoagulant at present in use for short-term therapy it is important to compare this drug with miradon. With phenindione, therapeutic levels are obtained within 24 to 48 hours (Sise *et al.*, 1957), although in the majority of patients these levels take 32 to 48 hours to be produced (Blaustein *et al.*, 1950). Coon *et al.* (1953) found that 18% of their patients were controlled at the end of 24 hours, 70% at 36 hours, and 95% at 48 hours. Our own experience with phenindione is in agreement with this finding.

With miradon, 56% of patients were found to have prothrombin times in the desired range of 10 to 20% prothrombin activity within 24 hours, and 30% were narrowly outside this control. The average time taken for production of maximal effect with miradon and phenindione is very similar (miradon 34 hours, phenindione 30 hours), and for the numbers considered the difference is not significant. With miradon, however, there is a narrower range of response to the initial loading dose (prothrombin activity 13-30% compared with phenindione, 16-49%). As compared with phenindione, therefore, the response to a given dose of miradon is a little more predictable. This allows a larger initial dose to be used with safety and leads to a greater number of patients in whom therapeutic levels of prothrombin time are produced within 24 hours. In addition, in the majority of patients, miradon produces some effect upon the prothrombin time within six hours, compared with 10 hours taken by phenindione. Control from

day to day appears very satisfactory with miradon, and only 14% of the estimations in this trial were not within the desired range. Our own experience with phenindione is very similar, and 15% of estimations have been found to be outside this control.

Sise *et al.* (1957) found on stopping phenindione that the prothrombin time of their patients returned to normal levels in 36 to 72 hours in the majority of patients. Miradon was found to take a similar period of time, and, as with phenindione (Guttas *et al.*, 1953), there was a rapid response to vitamin K₁.

It appears, therefore, that miradon has certain advantages over phenindione in the speed and predictability of initial response and subsequent rapidity with which therapeutic levels can be obtained. It is apparently just as readily managed from day to day, and has the advantage that a single dose produces striking uniformity of response, while most workers consider that phenindione requires to be given in divided daily doses to produce satisfactory uniformity of response (Blaustein *et al.*, 1950).

Summary

A new anticoagulant, miradon, has been assessed clinically and used therapeutically in the treatment of 25 patients requiring anticoagulant therapy.

The initial response to a loading dose of 300 mg. was rapid and some effect upon prothrombin time was evident in most subjects in six hours. Over 50% of patients had prothrombin levels within the desired therapeutic limits (prothrombin activity of 10 to 20%) at 24 hours, and 86% of subsequent estimations of the prothrombin time were within similar limits. Normal prothrombin levels were recorded between 36 and 72 hours after cessation of treatment and a very even response was evident during therapy. Vitamin K₁ produced a rapid reversal of anticoagulant action.

Compared with other anticoagulants miradon appears to approach more closely to the "ideals" for a short-term anticoagulant than other preparations at present in common use. The uniformity of response to a single daily dose suggests that it would prove satisfactory also in long-term therapy.

I thank Dr. A. Rae Gilchrist for his help and advice in conducting this trial, and Dr. C. P. Stewart for the laboratory facilities which he made available. I also thank Dr. R. M. Marquis and Dr. M. F. Oliver for criticism in preparing this paper. Miradon was generously supplied by Schering Corporation, who also provided an expense grant.

REFERENCES

- Blaustein, A. U., Croce, J. J., Alberian, M., and Richey, N. (1950). *Circulation*, 1, 1195.
- Bourgain, R., Todd, M., Herzig, L., and Wright, I. S. (1954). *Ibid.*, 10, 680.
- Brodie, B. B., Weiner, M., Burns, J. J., Simson, G., and Yale, E. K. (1952). *J. Pharmacol. exp. Ther.*, 106, 453.
- Burke, G. E., and Wright, I. S. (1951). *Circulation*, 3, 164.
- Butt, H. R., Allen, E. V., and Bollman, J. L. (1941). *Proc. Mayo Clin.*, 16, 388.
- Clatanoff, D. V., Triggs, P. O., and Meyer, O. O. (1954). *A.M.A. Arch. intern. Med.*, 94, 213.
- Coon, W. W., Duff, I. F., Hodgson, P. E., and Dennis, E. W. (1953). *Ann. Surg.*, 138, 467.
- Guttas, C. G., Moloney, W. C., and Sise, H. S. (1953). *Blood*, 8, 276.
- Hanson, H. H., Barker, N. W., and Mann, F. D. (1951). *Circulation*, 4, 844.
- Jaques, L. B., Gordon, E., and Lepp, E. (1950). *Canad. med. Ass. J.*, 62, 465.
- Overman, R. S., Stahmann, M. A., Sullivan, W. R., Huebner, C. F., Campbell, H. A., and Link, K. P. (1942). *J. biol. Chem.*, 142, 941.
- Prior, I. (1957). *N.Z. med. J.*, 56, 545.
- Quick, A. J. (1942). *The Hemorrhagic Diseases and the Physiology of Hemostasis*. Thomas, Springfield, Illinois.
- Scarrone, L. A., Beck, D. F., and Wright, I. S. (1952). *Circulation*, 6, 489.
- Sise, H. S., Maloney, W. C., and Guttas, C. G. (1957). *Amer. Heart J.*, 53, 132.
- Tulloch, J. A., and Gilchrist, A. R. (1951). *Ibid.*, 42, 864.
- Vander Veer, J. B., Funk, E. H., Boyer, F. R., and Keller, E. A. (1953). *Amer. J. Med.*, 14, 694.
- Weiner, M., Jimenez, M., and Katzka, I. (1956). *Circulation*, 13, 400.
- , Simson, G., Burns, J. J., Steele, J. M., and Brodie, B. B. (1953). *Amer. J. Med.*, 14, 689.
- Wright, I. S., and Prandoni, A. (1942). *J. Amer. med. Ass.*, 120, 1015.