Clinical Experience with a New Anticoagulant, Dipaxin (2-diphenylacetyl-1,3-indandione)

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Prothrombin levels as measured by the one-stage whole-plasma and the two-stage technics were followed in 80 patients receiving Dipaxin. The induction period is similar to that for Tromexan, namely, 48 to 60 hours and the recovery period 10 to 15 days which is somewhat longer than in the case of either Tromexan or Dicumarol. This recovery period is hastened to some degree by the administration of water-soluble vitamin K preparations and materially accelerated by vitamin K. The prothrombin level during maintenance therapy is unusually stable. Transient bleeding occurred in two patients. No other toxic effects were observed.

THE prevention of intravascular clotting has become of prime importance in the treatment of certain diseases. In a search for the ideal orally administered anticoagulant, numerous substances are being studied experimentally. In contrast, the clinical use of oral anticoagulants has been practically limited to the derivatives of coumarin (Dicumarol and Tromexan). Derivatives of 1,3 indandione have been receiving increasing clinical application. The hypoprothrombinemic effect of these substances was demonstrated in animals as early as 1944 by Kabat and associates, but since that time only a few reports of the clinical use of such drugs have been described. Of them, phenylindandione has received the greatest attention.

Correll studied numerous derivatives of 1,3 indandione experimentally, the most potent of them being 2-diphenylacetyl-1,3-indandione (Dipaxin). In a comparative experimental study of this drug with Dicumarol and Tromexan, Dipaxin was found to be 200 times as potent as Dicumarol and 1000 times stronger than Tromexan. It was also found to have an induction period as short as that of Tromexan and to have the sustained hypoprothrombinemic effect of Dicumarol. Vitamin K was found to be an adequate antidote against the Dipaxin induced prothrombinopenia. Recently Field, Goldfarb, Ware and Griffith reported satisfactory lowering of the prothrombin in control patients and those having evidence of intravascular clotting. They observed no toxic effects in the approximately 110 cases observed. The purpose of this paper is to report our experience with the use of Dipaxin in 80 patients.

METHODS

Blood prothrombin levels were determined in all patients by the two-stage method of Warner, Brinkhous and Smith as modified by Ware and Seegers. In each instance a one-stage determination was also carried out, the original technic of Quick being followed with the exception that Soluplastin was used as thromboplastin in place of rabbit brain extract. In our hands this has been found to be quite stable and yields relative uniform curves from lot to lot. In the following pages wherever prothrombin or prothrombin level is mentioned without specific designation of the one-stage or two-stage technic the latter will be understood. This method is used routinely in our laboratory for the control of all prothrombin depressants.

The effect of Dipaxin was studied on 80 patients from the wards of the Presbyterian and the Cook County Hospitals. Until after the completion of this study we had no information on the use of the drug in human beings, and it was deemed necessary to proceed with caution. It was also considered important to observe the effect of a single dose of the drug from the point of view of the induction period, the degree of hypoprothrombinemia produced and the length of time such an effect was maintained. Accordingly, 30 patients received single doses of

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* Kindly supplied by Dr. E. W. Blanchard of Schefflin & Co.
† Kindly furnished by Dr. H. F. Hailman of the Upjohn Co.
Dipaxin varying from 1 to 25 mg. (Two patients were given 1 mg. each; two were given 1.5 mg.; five patients were given 3 mg.; three patients were given 4 mg.; five patients were given 5 mg.; two patients were given 8 mg.; one was given 10 mg.; four patients were given 12 mg.; four patients were given 15 mg.; and two patients were given 25 mg. each.) The prothrombin levels were measured daily or every second day for from 5 to 18 days following the administration of the drug.

In order to determine the safety of repeated doses of the drug five patients were given Dipaxin intermittently and observed for cumulative effects. Doses of Dipaxin were given at two to four day intervals.

The remaining 45 patients were given initial doses of 15, 20 and 25 mg. and subsequent daily doses to attain a therapeutic level as rapidly as possible. These patients were maintained on the drug for periods of time varying from 4 to 182 days. Twenty-seven were on the drug for at least two weeks, 20 for three weeks, 11 for four weeks, 7 for five weeks, 5 for six weeks and 2 patients for over eight weeks. One patient took the drug for over five months. Three of the 45 patients were followed, during part of their course, as out patients. Prothrombin levels were measured usually daily for the first two weeks then every two to five days subsequently. The one long-term case eventually reported for examination at two-week intervals. There were 12 patients in the maintenance therapy group who were allowed to recover spontaneously and were followed for 3 to 21 days after withdrawal of the drug.

In five patients who received Dipaxin for a minimum of three weeks the following liver function tests were done at the end of the administration of the drug: cephalin flocculation, thymol turbidity, gamma globulin, cholesterol, alkaline phosphatase, total protein and icterus index.

Seven patients were given 72 mg. of Hykinone intravenously (24 mg. in each of three injections at 30-minute intervals) 24 hours after the last dose of the drug. Two additional patients were given 288 mg. of Hykinone intravenously over a two-hour period. One patient with a prothrombin of 4 per cent and bleeding from the gastrointestinal tract was given 50 mg. of Hykinone intravenously daily for three days in addition to 500 cc. of whole blood. Another patient, in order that surgery might be safely carried out, was given intravenous doses of 72, 50 and 50 mg. of Hykinone, respectively, on successive days. Three patients were given 500 mg. of K-analogue* intravenously over a two-hour period. Varying doses of vitamin K₁ (Mephyton)† were given to six patients who had been maintained on Dipaxin for less than two weeks. Three of these patients received the drug orally in doses of 50, 100 and 150 mg. respectively. Two patients were given K₁ intravenously by infusion over a two-hour period, one receiving 50 mg. the other 100 mg. The sixth patient, who had gross hematuria, was given 50 mg. orally and 100 mg. intravenously on the same day.

In an effort to compare the effects of certain of the prothrombin depressing drugs in the same patient, seven patients were given successive courses of Dipaxin, Tromexan and Dicumarol after sufficient time had elapsed for the prothrombin level to return to normal following withdrawal of each drug.

**Results**

**Effects of Single Doses of Dipaxin.** Those patients who received 1 or 1.5 mg. of Dipaxin showed no significant change in their prothrombin level. Five patients who were given a single dose of 3 mg. showed a distinct lowering, (fig. 1A), the average decrease in prothrombin percentage being 34 per cent as measured by the two-stage test and 28 per cent by the one-stage. The lowest level (63 per cent) was observed at approximately 36 to 40 hours after the administration of the drug. The depression measured by the two-stage method was sustained for two days and then returned to the pretreatment levels. The composite effects of 5 mg. dosages of Dipaxin are seen in figure 1B. The drop in prothrombin level was less than 10 per cent as measured by both the two-stage and one-stage prothrombin tests. In the three patients who were given either 8 or 10 mg. the drop in the two-stage prothrombin level was 35 to 44 per cent and the one-stage prothrombin level fell from 24 to 51 per cent. These drops (to levels as low as 48 per cent) occurred within the first 40 hours following the ingestion of the drug. The average effect on the prothrombin level in four patients given 12 mg. of Dipaxin is shown in figure 1C. The depression was 41 per cent as measured by the two-stage and 24 per cent by the one-stage test. The most rapid lowering came in the first 24 hours and the prothrombin continued to fall during the next two days. Unlike the change in the instances of the lower doses where a rather prompt rise occurred after the nadir, these patients maintained a lowered prothrombin level for longer than the seven days. The effect of a single dose of 15 mg. of Dipaxin on four patients is seen in figure 1D. The composite of

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* Kindly supplied by Dr. H. F. Hailman of the Upjohn Co.
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Fig. 1. The above group of graphs represents the effects of varying single doses of Dipaxin on the prothrombin levels (two-stage) of human beings. (A) This chart shows the composite response of five patients who received 3 mg each. As measured by the one-stage test there was a drop of 28 per cent and by the two-stage a drop of 34 per cent (to 63 per cent) in 36 hours. (B) Strangely enough, the five patients who were each given 5 mg of Dipaxin showed less of a prothrombin depression than those given 3 mg each, 10 per cent being the average drop. (C) The four patients receiving 12 mg each showed an average lowering of 41 per cent, the greatest drop occurring in the first 24 hours and the fall continuing for the next two days. Unlike the change in the instances of the lower doses, where a rather prompt rise occurred after the nadir, these patients maintained a lowered level for longer than seven days. (D) The four patients who were given 15 mg each showed an average drop of 51 per cent, the lowest level of 47 per cent occurring in about 40 hours. As in the case of the 12 mg dose, the prothrombin remained depressed over the seven-day observed period. (E) The two patients receiving 25 mg each showed a maximum average drop of 39 per cent the lowest level (35 per cent) being reached in 40 hours.

Fig. 2. The above graphs represent the composite course of 25 patients who were maintained on continuous Dipaxin therapy for a minimum of three weeks. The chart on the left shows the prothrombin levels as measured by the two-stage test and on the right the corresponding one-stage levels are shown. The heavy line in each graph indicates the average course and the shaded area the limits of individual determinations on respective days. Note that the prothrombin as shown by the one-stage test drops more promptly than that measured by the two-stage and then returns to and remains at a higher level throughout the course of the therapy. There were also wider variations in the one-stage estimations than in the two-stage.
the prothrombin percentages of these patients reveals an overall drop of 51 per cent in the two-stage and 15 per cent in the one-stage determinations. The prothrombin level remained depressed over the observed period of seven days. The change in the prothrombin percentage in two patients after receiving 25 mg. of Dipaxin orally is seen in figure 1E. In these patients there was a maximum drop in the prothrombin level of 39 per cent in the two-stage and 40 per cent in the one-stage test, the greatest fall being in the first 40 hours with a further decrease in prothrombin level over the next two days.

**Maintained Dipaxin Therapy.** Twenty patients had initial doses of 20 mg. and 22 patients received 25 mg. In three patients with prothrombin percentages in the 70's both by the two-stage and one-stage prothrombin tests, the initial dose of Dipaxin was 15 mg. Subsequent dosage was dictated by the change in the two-stage prothrombin level. If the prothrombin percentage was between 50 and 80 per cent, 15 mg. were given, if it was between 35 and 50 per cent, 10 mg. and if the prothrombin was 20 to 35 per cent, 5 mg. of Dipaxin were administered; when the prothrombin levels were 15 to 20 per cent, 1 to 3 mg. of the drug were given. If during the induction period the prothrombin level fell rapidly to below 30 per cent the drug was withheld or a very small dose was given (1 to 2 mg.). This modification of dosage scheme was followed also during maintenance therapy whenever there was a rapid drop in the prothrombin percentage. The course of 25 patients over a three-week period is summarized in composite graphs shown in figure 2. The therapeutic prothrombin level was attained in an average of 60 hours the range being 40 to 96 hours. The lowest levels usually occurred between the sixth and eighth days. After the initial administration of the drug the average doses for the second, third and fourth day decreased progressively to 14, 8 and 6 mg. The maintained dose was, on the average, 3 to 5 mg. daily, the range being 0 to 7 mg.

The one-stage level in the early period (first two to three days) dropped more rapidly than the two-stage level, after which the latter was, for the most part, slightly lower than the one-stage throughout. This is comparable to the observed behavior of the two tests in patients given Dicumarol or Tromexan. Following the withdrawal of the drug there was a very slow rise in the prothrombin level, the return to normal or near normal requiring 15 to 20 days.

In contrast to this is seen the more rapid increase in the prothrombin level following the administration of vitamin K derivatives. The summation of the prothrombin levels of the seven patients who received 72 mg. of Hykinone is shown in figure 3. The prothrombin level is seen to increase steadily during the following four days. These patients had an average prothrombin that was below the lower limit of the therapeutic bracket, and within 16 hours the average level of the prothrombin had increased to the therapeutic range. The two patients who received 288 mg. of Hykinone by intravenous infusion were within the thera-
peutic bracket, and their response is also shown in figure 3. The prothrombin rose from 24 to 34 per cent in 24 hours and dropped to 29 per cent at the end of 48 hours.

The effect of the intravenous administration of 500 mg. of K-analogue on induced hypopro-

VITAMIN K₁

![Graph showing prothrombin levels for vitamin K₁](image)

Fig. 4. The above graphs show the response of individual patients on maintained Dipaxin therapy to single oral doses of vitamin K₁. Each patient had been on the drug for eight days. The first had received a total of 68 mg. of Dipaxin, the second 85 mg. and the third 76 mg. All were within the therapeutic bracket when the vitamin K₁ was given and all showed a prompt rise of approximately 20 to 30 per cent in 24 hours.

VITAMIN K₁

![Graph showing prothrombin levels for vitamin K₁](image)

Fig. 5. This chart shows the effect of vitamin K₁ given intravenously to patients with Dipaxin produced hypoprothrombinemia. The responses are similar to those occurring when the vitamin was given orally, though the 24-hour rise in the case of the patient receiving 100 mg. intravenously was considerably greater than in patients getting the drug orally. The pair of lines on the right shows the response of a patient to combined oral and intravenous vitamin K₁. This patient had hematuria and lumbar pain when the drug was given and her prothrombin was less than 1 per cent of normal. The pain and bleeding stopped 15 hours after the vitamin was given. The first patient had been given 61 mg. of Dipaxin in eight days, the second 49 mg. in six days and the patient with the hematuria had received 190 mg. over a period of 35 days.

thrombinemia in three patients is also shown in figure 3. The prothrombin level was followed for two days and showed an increase similar to that seen following the administration of 72 mg. of Hykinone.

Vitamin K₁ brought about the most rapid rate of recovery in the prothrombin level. In the few cases observed the drug (fig. 4) appeared to be slightly less effective when given orally than when administered by the intravenous route (fig. 5). In one patient who received 100 mg. of vitamin K₁ intravenously the prothrombin rose from 12 to 64 per cent within 20 hours (fig. 5).

Comparison of Dipaxin, Tromexan and Dicumarol

The composite responses of seven patients each receiving Dipaxin, Tromexan and Dicumarol successively and in that order are shown in figure 6. The rate of induction of the prothrombinopenic levels are similar for Dipaxin and Tromexan. The therapeutic level was attained with these drugs in approximately 60 hours. In the case of Dicumarol the therapeutic level had not quite been reached at the end of 96 hours. One patient was more resistant than the other six. Higher doses of Dipaxin and Tromexan than usual were necessary adequately to suppress the prothrombin level.

![Graph showing composite responses of seven patients](image)

Fig. 6. The above graphs represent the composite responses of seven patients who were given successive courses of Dipaxin, Tromexan and Dicumarol, sufficient time being allowed between courses for the prothrombin levels to return to normal. In the case of Tromexan and Dipaxin the therapeutic level was reached between 48 and 72 hours after the drug was started. The average prothrombin level of the patients when receiving Dicumarol had not quite reached the therapeutic bracket 96 hours after the drug was started. All points represent two-stage prothrombin levels.
Even large doses of Dicumarol did not effect an adequate decrease in the prothrombin level after one week.

**Toxicity**

The liver function tests carried out on five patients who received Dipaxin for a minimum of three weeks showed no significant variations from the normal. No untoward clinical signs or symptoms other than bleeding were observed in any of the patients taking Dipaxin.

**Discussion**

The criteria for the evaluation of any prothrombin depressant are safety, effectiveness, economy and convenience in descending order of importance. No drug available at the present time meets these requirements satisfactorily. From the foregoing data, Dipaxin would appear to fulfill them to an extent similar to that of its predecessors. Of the drugs used clinically to date, it is the most potent, hence the required dosage is the lowest. The induction rate is similar to that of Tromexan and shorter than that of Dicumarol. Patients receiving it are readily controlled within the therapeutic prothrombin bracket and are easily maintained within that bracket over a period of time. Once the therapeutic level is achieved the prothrombin is reasonably stable, more so, in our experience, than in the case of patients receiving Dicumarol or Tromexan. This, no doubt, is related to the character of the recovery period which is somewhat longer than that of Dicumarol-treated patients. It is considerably longer than that of Tromexan, the latter requiring 24 to 48 hours while most patients receiving Dipaxin did not show a near normal prothrombin until 15 to 20 days following withdrawal of the drug. The recovery period in patients receiving Dicumarol is about one-half that time. This is both an advantage and disadvantage. It insures a steadily controlled patient despite an occasional accidental omission of the daily dose. It has the disadvantage of a slow recovery when a rapid return towards normal is desired for unexpected surgery, in the case of injury or when an unusually low prothrombin level and bleeding occur. This slow recovery period is in all probability also related to the relative ineffectiveness of the standard vitamin K preparations in counteracting the prothrombinopenic action of the drug. And these three characteristic effects of the drug—stable therapeutic prothrombin bracket, slow recovery period and resistance to standard vitamin K active substances—are undoubtedly based on a cumulative action greater than that of the two other drugs. The rapid action of vitamin K$_1$ in neutralizing the effects of the drug insures its safety.

The incidence of bleeding in our series (slightly more than 2 per cent) was less than that which we have observed with Tromexan and Dicumarol. There have been fewer patients whose prothrombin levels were below the therapeutic bracket for any period of time, and this may be the sole reason for the lowered incidence of hemorrhage. It is also possible that other factors such as capillary fragility are less altered. The one patient in whom bleeding was definitely attributed to the effect of Dipaxin responded promptly to vitamin K$_1$, and the hematuria and symptoms disappeared within 24 hours after the vitamin was given.

From our study, the possibility of hemorrhage would appear to be the only hazard in the administration of the drug. There were no other apparent toxic effects, subjectively or objectively. Except for an occasional complaint of nausea with a large dose the same may be said of Dicumarol. Dermatitis which has occasionally accompanied the use of Tromexan has not been observed with Dicumarol or Dipaxin. As a result of our early studies on Dicumarol we have used the two-stage prothrombin assay routinely for the control of prothrombin depressants. While it is a more complicated procedure, it reflects, we believe, a more accurate prothrombin level and hence provides a more safely controlled patient from the points of view of both clotting and bleeding. Inasmuch as the one-stage method is a less complicated test and is more widely used, we believe that it should be evaluated in connection with each prothrombin depressant studied. Modifications of the one-stage test from time to time may alter its relationship to the two-stage test and to anticoagulant ther-
apy in general, a point of particular importance in the control of any prothrombin depressant.

In previous studies on Dicumarol we have found the results of the one-stage technique in some patients to vary widely from those of the two-stage.\textsuperscript{10-12} A recent survey of our data covering the use of Dicumarol in patients in whom both tests were run in parallel showed this to be true in approximately 73 per cent of the cases.* In a recently completed study on Tromexan 51 per cent of 116 patients showed such a variation.\textsuperscript{13} It was true of Dipaxin in 32 per cent of the 80 patients studied. From this point of view, Dipaxin would appear to be a safer drug. The possible causes of such variation have been discussed in earlier communications and will not be taken up here. They are still poorly understood. As in the case of the other drugs\textsuperscript{11, 13} levels determined by the one-stage method show an earlier drop than those found by the two-stage and after the first few days assume a position 10 to 20 points above the level of the two-stage method.

The results of Field, Goldfarb, Ware and Griffith\textsuperscript{4} are similar to those recorded here with the following notable exceptions: (1) In our experience the return of the prothrombin to normal after the withdrawal of Dipaxin is considerably longer than that observed in their patients (15 to 20 days as compared with 3 to 6). (2) In our series water-soluble vitamin K active substances only slightly affected the hypoprothrombinemia produced by Dipaxin; this is in accord with the findings of Correll and coworkers.\textsuperscript{3} The disparity in the first instance is not clear. The difference in the responses to water-soluble vitamin K preparations may result from the fact that our cases had had repeated doses of Dipaxin and only one day of vitamin K dosage, whereas the cases of Field and coworkers received a single dose of Dipaxin and vitamin K over a number of successive days. They also administered the vitamin intramuscularly whereas our patients received it intravenously. In their discussion they note that the induction period is greater than that of Dicumarol, a finding contrary to ours though the actual time observed, 48 to 60 hours, is very similar to that seen in our patients. In our experience Dicumarol requires a longer period to produce its maximum effect.

We have had insufficient experience with Cumopyron and phenylindandione to compare them with Dipaxin, Tromexan and Dicumarol.

As yet we have had little experience with the use of Dipaxin in patients with thromboembolism. Since, however, it is effective in controlling the prothrombin level in a uniform and safe manner one would expect it to be a satisfactory drug for the treatment of such conditions.

**Summary**

1. The drug 2-diphenylacetyl-1,3-indandione (Dipaxin) has been used to reduce the prothrombin level in 80 patients, most of them suffering from conditions other than thromboembolism.

2. It is an effective prothrombin depressant, serving to reduce that coagulation factor to a therapeutic level in 48 to 60 hours and to maintain such a level uniformly over a period of weeks.

3. The recovery period after the withdrawal of the drug is 15 to 20 days, somewhat longer than that following Tromexan or Dicumarol.

4. This recovery is hastened to some degree by the administration of the standard vitamin K preparations and materially accelerated by vitamin K\textsubscript{1}.

5. Bleeding occurred in two patients, an incidence of slightly more than 2 per cent. In the one patient in whom it could definitely be attributed to the lowered prothrombin the hematuria ceased within 24 hours after vitamin K\textsubscript{1} oxide was administered, the prothrombin returning towards normal during that period of time. There were no other toxic effects observed.

6. As in patients receiving Dicumarol or Tromexan variations between the prothrombin levels as measured by the one-stage and two-stage tests were present to a significant degree. The implications of these variations are discussed.

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* In most of these instances acetone-dried rabbit brain was used as the thromboplastin. In a small number of cases in which Soluplastin has been employed it has been our impression that this has been present to a lower degree.
Sumario Español

Niveles de protrombina determinados por las técnicas de una etapa en plasma íntegra y de dos etapas fueron determinados en 80 pacientes que se les administraba "dipaxin." El período de inducción es similar al de "tromexan," o sea, 48 a 60 horas y un período de recuperación de 10 a 15 días el cual es algo más largo que el de "tromexan" o dicumarol. Este periodo de recobro es aligerado en algún grado por la administración de preparaciones aquaremolables de vitamina K y materialmente acelerado por vitamina K₁. El nivel de protrombina durante la terapia sostenida es remarcablemente estable. Sangrías transitorias ocurrieron en dos pacientes. Ningún otro efecto tóxico fue observado.

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