Clinical Experience with Dipaxin and with the Combined Use of Prothrombopenic Agents

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The experience with a new prothrombopenic agent, Dipaxin, is presented. With a 30 mg. dose a prothrombin complex concentration under 30 per cent is reached in 41 hours or less. When associated with 1500 mg. of Tromexan the latent period is reduced to 24 hours. The prothrombopenic action of Dipaxin is readily counteracted with vitamin K, administered either orally or intravenously.

Anticoagulant therapy has its main indication during the acute phase of thromboembolic disease. Among the drugs with anticoagulant properties the most commonly used are those which interfere with the synthesis of prothrombin and stable factor, the so-called prothrombopenic agents.

We have had a large personal experience with bishydroxycoumarin (Dicumarol), ethyl biscoumacetate (Tromexan), cyclocumarol (Cumopyran) and phenindione (Danilone). From these, we consider Danilone the drug of choice as its action starts in a relatively short time (36 to 48 hours) and the initial and maintenance doses are very similar in different individuals.

Many efforts have been directed towards the finding of a prothrombopenic agent with a quicker action and a more reproducible dosage. We have studied a new indandione derivative the 2-diphenylacetyl-1,3-indandione (Dipaxin) which appears to meet the above mentioned characteristics and are presenting in this paper our observations.

Drugs used in this study were made available through the courtesy of Abbott Laboratories, North Chicago, Ill., (Dicumarol and Cumopyran); J. R. Geigy, Basel, Switzerland (Tromexan), Charles E. Frosst and Co., Montreal, Canada (Danilone), Dr. H. F. Hailman from the Upjohn Co., Kalamazoo, Mich. (Dipaxin), Hoffmann-La Roche, Basel, Switzerland (Synkavit and Konakion), and Merck and Co. Inc., Rahway, N. J. (Mephyton).

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Correll and co-workers have reported that out of a group of compounds including Dicumarol, Tromexan and 17 analogs of the indandione group, Dipaxin has the greatest prothrombopenic action on rabbits. Field and associates and Duff and colleagues have administered Dipaxin to human subjects without observing any toxic effects. They consider this drug more potent than any other oral anticoagulant with which they have had experience. The former workers recommended an initial dose of 30 mg. and the latter a dose of between 30 to 75 mg. From their study on the use of Dipaxin in 80 patients, Pascale and Olwin concluded that it is an effective prothrombin depressant serving to reduce this coagulation factor to an effective therapeutic level in 48 to 60 hours.

The structure of Dipaxin is shown in figure 1.

Methods

Blood prothrombin complex concentration was measured according to the one-stage method of Quick. In some instances the procedure of Owren was used to measure the activity of prothrombin and stable factor (proconvertin) and of both factors combined. Labile factor was determined by Stefani's method. Human brain thromboplastin prepared according to Owren was used throughout.

Study and Results

Effect of a Single Dose of Dipaxin

The action of a single dose of 30 mg. of Dipaxin administered orally was studied in 10 individuals who did not present any liver,
kidney or hematological disturbance. These results are shown in figure 2.

It can be observed easily that the action of Dipaxin on the prothrombin complex* is already evident at the seventeenth hour. At the twenty-fourth hour, 5 out of 10 subjects showed a prothrombin complex concentration below 30 per cent, that is to say a useful therapeutic level. In the remaining five the values were between 32 and 44 per cent. At the forty first hour all the controls showed useful prothrombin complex levels between 8 and 28 per cent, which lasted for about 100 hours. A quicker effect could not be obtained by increasing the dose up to 40 mg.

Comparison of Dipaxin with Danilone and Tromexan

The effect of a single dose of Dipaxin compared favorably with that of an equivalent single dose of Danilone. After 300 mg. of the latter none of the 10 subjects studied showed a prothrombin complex concentration below 30 per cent at the twenty fourth hour, and only in eight was this level obtained by the thirty sixth hour. In the remaining two this level was never obtained (fig. 3).

When the prothrombopenic actions of Dipaxin and Tromexan are compared, the results are very similar although the latter shows a slightly faster effect. This is demonstrated in the five illustrative examples shown in figure 4. All these cases had a prothrombin complex concentration below 34 per cent 24 hours after a single dose of 1500 mg. of Tromexan.

Effect of Sodium Menadiol Diphosphate (Synkavit) and Fitilmenadione (Vitamin K₁) on the Hypoprothrombinemia Induced by Dipaxin

Two patients under treatment with Dipaxin in whom the prothrombin complex had been reduced below 25 per cent, received 30 mg. of

* Prothrombin complex concentration applies to the values obtained by the method of Quick.
Synkavit intravenously, with no demonstrable effect on the prothrombin complex during the following 24 hours (fig. 5). This may appear to be too low a dose but the same lack of response was observed by Pascale and Olwin with much larger doses. In one patient the last dose of Dipaxin had been given 36 hours before the Synkavit injection and in the other, 42 hours before.

Two other patients under treatment with Dipaxin in whom the prothrombin complex had been reduced below 25 per cent, received 50 mg. of vitamin K1 (Mephyton) intravenously. The prothrombin complex values rose significantly during the following hours being above 45 per cent at the fourth hour and reaching the pretreatment values in 24 hours. In one patient the last dose of Dipaxin had been given 17 hours before the vitamin K1 injection and in the other 42 hours before (fig. 5). Such high intravenous doses of Mephyton have the serious drawback of conditioning a refractory period during which the patient does not respond to new doses of the prothrombopénic agent. Occasionally a dangerous prothrombin complex level occurs during treatment with Dipaxin as with other prothrombopénic drugs. It is our experience that under these circumstances, the administration of a small dose (3 to 5 mg.) of vitamin K1 (Konakion) by mouth rapidly brings the prothrombin complex to safe values without rendering the patient refractory to the continuation of treatment.

**Use of Dipaxin in Thromboembolic Disease**

Dipaxin has been used in 60 cases of thromboembolic disease. An initial dose of 30 mg. was administered and all the cases showed a prothrombin complex concentration below 30 per cent on the second day. The maintenance dosage depends on the patients' individual reaction to the drug, but it is fairly constant and it fluctuates between 3 and 5 mg. per day. Only 14 per cent of our cases under prolonged treatment presented in some of the determinations prothrombin complex concentrations above 35 per cent. This figure is similar to the one reported by us for Danilone (16 per cent) and better than those for Dicumarol (30 per cent) and Tromexan (53 per cent). Transient hematuria was the only hemorrhagic episode in this series (1.7 per cent).

According to our experience, the anticoagulant treatment of thromboembolic disease with Dipaxin has the same beneficial effects as Dicumarol, Danilone and Tromexan.

**Effect of Dipaxin on the Components of the Prothrombin Complex**

No depression of the concentration of the labile factor was observed in any of the patients treated with Dipaxin in whom this component was determined. This lack of effect on the labile factor has been also observed for Dicumarol, Tromexan and Danilone.

![Fig. 4](image1.png)

**Fig. 4.** Effect of a single 1500 mg. dose of Tromexan, administered orally, on the prothrombin complex concentration in five individuals.

![Fig. 5](image2.png)

**Fig. 5.** Effect of a 30 mg. dose of sodium menadiol diphosphate (Synkavit), dotted line, and a 50 mg. dose of fitilmenadione (vitamin K1), solid line, administered intravenously on the hypoprothrombinaemia induced by Dipaxin.
The concentration of prothrombin, of stable factor (proconvertin), and of prothrombin and stable factor (proconvertin) combined was also measured in all 60 patients under treatment with Dipaxin for thromboembolic disease. The behavior of these factors was similar to that observed during treatment with other prothrombopenic drugs. In most patients stable factor is definitely depressed, reaching values of less than 30 per cent 24 hours after starting the treatment. The reduction of the prothrombin concentration is slower and values around 30 per cent are observed only after four or five days of treatment have elapsed. The behavior of prothrombin and stable factor combined is similar to that of the prothrombin complex concentration measured by the method of Quick, with some differences which will be described in detail in a separate communication.

The Combined Use of Prothrombopenic Agents

Our experience as well as that of others shows that Tromexan has an earlier prothrombopenic effect than other similar drugs. Nevertheless prolonged treatment with Tromexan presents serious disadvantages, since the daily dose varies widely in different and even in the same patient. This accounts for a higher proportion of values beyond the therapeutic margin. Trying to eliminate this drawback while profiting from its earlier effect, Tromexan has been used in combination with other prothrombopenic agents for the initial dose.

In 10 patients 1500 mg. of Tromexan and 30 mg. of Dipaxin were simultaneously given. The prothrombin complex measured exactly 24 hours after was between 37 and 17 per cent as shown in figure 6. The maintenance treatment was followed with Dipaxin alone and the patients reacted in the same way as when receiving Dipaxin without Tromexan. In none of the 10 patients was it necessary to give the prothrombopenic agent on the second day.

In another 10 patients 1500 mg. of Tromexan and 200 mg. of Danilone were simultaneously given. The prothrombin complex measured exactly 24 hours after was between 50 and 17 per cent.

The association of Tromexan with Dipaxin produces an earlier useful prothrombin complex depression, which does not reach dangerous levels with the dosage used. After this combined initial dose, treatment is continued as if only one agent had been given.

DISCUSSION

The data presented above show that Dipaxin is a potent prothrombopenic agent. In all our cases the therapeutic level was reached between 24 and 41 hours after a 30 mg. initial dose. This contrasts with the experience of Pascale and Olwin who observed this result in an average of 60 hours. This discrepancy is probably due to our larger initial dose of 30 mg. as compared with their dose of 25 mg. The average values of Pascale and Olwin for the one-stage prothrombin method are slightly higher than those for the two-stage method. In our hands Dipaxin has shown a definitely earlier effect than Dicumarol, a finding contrary to that of Field and co-workers which can be explained by the lower initial dose they used. The daily maintenance dose of Dipaxin fluctuates very little in the same patient and even in different individuals, being on the average 3 to 5 mg. This is the same dose used by Pascale and Olwin and very similar to that of Field and colleagues.

The recovery period of the prothrombin complex after withdrawal of Dipaxin is longer than that for Tromexan, Danilone and Dicumarol. Most of our patients reach a
pretreatment level of prothrombin complex 132 hours after a single dose of Danilone and 156 hours after a single dose of Dieumarol. On the contrary, none of our cases had attained the pretreatment level 139 hours after a single dose of Dipaxin. Cyclocumarol (Cumopyran) has even a longer recovery period than Dipaxin, being of about 13 days according to our experience. The apparent disadvantages of this long recovery period of Dipaxin is counteracted by the clear-cut antagonism of vitamin K₁. Small oral doses are sufficient to bring back to safe values exaggeratedly reduced prothrombin complex concentrations without rendering the patient refractory to the continuation of treatment. With high intravenous doses a rapid normalization of the prothrombin complex is obtained.

One of the main disadvantages of the anticoagulant treatment with prothrombopenic drugs is the long period of time necessary to obtain a therapeutic prothrombin complex level. This makes the administration of heparin necessary during the first two or three days after the embolic episode. When Dipaxin, a relatively slow acting prothrombopenic drug, is given in combination with Tromexan for the initial dose, a useful level of prothrombin complex is always obtained within 24 hours. This permits the withdrawal of heparin after the first day which is both convenient and economical. When using Dipaxin and Tromexan, the recommended doses are 30 and 1500 mg., respectively. When the treatment is started with this combination, the prothrombin complex values do not reach dangerous levels and the doses for the following days are given according to the usual schedule. The combination of prothrombopenic agents has been used by Shapiro to initiate the treatment in order to eliminate the possibility of resistance to one of the drugs.

**Summary and Conclusions**

Dipaxin is a potent prothrombopenic agent. With an initial dose of 30 mg. the prothrombin complex reaches therapeutic levels within 41 hours. The maintenance doses vary very little in different and in the same patient (3 to 5 mg. daily).

When compared with Tromexan and Danilone the induction period of Dipaxin is longer than that of the former and shorter than that of the latter.

Vitamin K₁ readily counteracts the prothrombopenic action of Dipaxin. Small doses are effective in bringing the prothrombin complex from dangerous to safe values and large intravenous doses rapidly restore the prothrombin complex to normal.

Dipaxin acts first on the stable component and only later on the prothrombin itself.

The clinical results obtained during the anticoagulant treatment with Dipaxin are similar to those observed with other prothrombopenic drugs. The incidence of hemorrhage in our series was only 1.76 per cent. No other untoward effects were observed.

The combination of 1500 mg. of Tromexan and 30 mg. of Dipaxin for the initial dose results in a therapeutic prothrombin complex level at the twenty fourth hour. This has the great advantage of limiting the use of heparin only to the first day of treatment. After this combined initial dose, no dangerous level of prothrombin complex has been observed and the future therapeutic schedule is not changed.

**Sumario Español**

Se da cuenta de la experiencia con Dipaxin un nuevo y potente agente protrombopénico. Con una dosis inicial de 30 mg. se obtienen en 41 horas valores de complejo protrombínico dentro de límites terapéuticos. La dosis diaria de mantención es muy poco variable y oscila entre 3 y 5 mg.

Comparado el Dipaxin con el Dieumarol y el Tromexan demuestra tener una acción más rápida que el primero y más lenta que el segundo.

La vitamina K₁ es un antagonista eficaz de la acción protrombopénica del Dipaxin: pequeñas dosis por vía oral lleva los valores de complejo protrombínico de límites peligrosos al margen terapéutico; dosis altas por vía endovenosa neutraliza rápidamente los valores.

El efecto del Dipaxin se ejerce primeramente sobre el factor estable y sólo más tarde sobre la protrombina propiamente tal.

Los resultados obtenidos con el Dipaxin en
el tratamiento de la enfermedad tromboembrólico son similares a los ya conocidos con otros agentes protrombopénicos. Como complicación en nuestra serie se presentó un 1,76 por ciento de hemorragias.

La combinación de la dosis inicial de 30 mg. de Dipaxin con 1500 mg. de Tromexan lleva a valores de complejo protrombínico bajo 30 por ciento en 24 horas, lo cual tiene la ventaja de limitar el uso de la heparina al primer día de tratamiento. Con esta dosis combinada no se han apreciado valores peligrosos de complejo protrombínico y el tratamiento puede continuar con Dipaxin solo según el esquema habitual.

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