Clinical Evaluation of a New Oral Anticoagulant "Sintrom"

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The clinical results in 100 patients treated for thromboembolic disorders were compared with 100 similar patients treated with Dicumarol. The rate of induction, ability to maintain a constant therapeutic level, and duration of action were especially considered. Induction and maintenance dosage were determined by clinical trial.

Since the introduction of Dicumarol into clinical usage in 1942, the efficacy of anticoagulant therapy for the treatment of thromboembolic disorders has been well established. The search for more efficient prothrombin depressants has continued and the clinical usefulness of many such drugs has been investigated. Those that have been found acceptable thus far have all been either coumarin or indanedione derivatives. It is the purpose of this paper to report 1 year's experience with a new derivative of the coumarin series, nitrophenyl-acetyl-ethyl-4-oxycoumarin. This drug is known commercially as Sintrom.*

The mode of action and metabolism of Sintrom have been thoroughly studied by European workers and they have found that its main action is to depress factor VII and to a lesser extent prothrombin, early in the course of treatment.1 Both are equally affected after several weeks of treatment.2 It disappears from the body rapidly but unlike ethyl biscoumacetate (Tromexan), which is metabolized to an inactive acid form, Sintrom is chiefly excreted unaltered.3-5 Preliminary clinical studies indicated that Sintrom is intermediate in action between Tromexan and Dicumarol1-3.5-9 and suggested that it has certain advantages over both of them. Other workers10-12 in this field have listed the qualities of an ideal anticoagulating agent and it is generally agreed that, could these criteria be met, the clinical application and safety of these drugs would be increased. We consider the following to be the most important qualities that a drug of this type should possess: 1. It should rapidly lower the activity of the prothrombin complex to a therapeutic range. 2. It should maintain its effect long enough to prevent fluctuations of prothrombin levels when the drug is administered in single daily doses. 3. It should be metabolized or excreted quickly enough to permit a rapid recovery of the prothrombin complex on cessation of therapy. 4. Its effect should be rapidly counteracted by the administration of a suitable pharmacologic antagonist. 5. The doses should be relatively constant in a given patient and from patient to patient. 6. It should be effective when administered orally. 7. It should be nontoxic and well tolerated in therapeutic dosages. With these factors in mind a clinical study was undertaken at the Pennsylvania Hospital to evaluate the efficacy of Sintrom as an anticoagulant and to compare it with other coumarin drugs.

Methods and Materials

During the period of this study 156 patients with thromboembolic disorders received Sintrom. These cases were unselected and consisted of all patients admitted during this period who required anticoagulant therapy. Those cases with thrombophlebitis, pulmonary embolism, and arterial embolism, received heparin initially as well, in order to produce an immediate anticoagulant effect. Early in this study there were 35 patients who were treated initially with Dicumarol. When each patient's average maintenance dose was established, Sintrom was substituted in an attempt to establish an equivalence in dosage between these 2 drugs. We found that 2 mg. of Sintrom are usually equivalent to 25 mg. of Dicumarol in prothrombin-depressant activity.

In our hospital the responsibility for the administration of anticoagulant drugs has been delegated

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* The supply of Sintrom used in this study was kindly furnished by Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, N. Y.
to the anticoagulant team of the Cardiovascular Department. We consider the generally accepted therapeutic range of 10 to 30 per cent prothrombin activity as an adequate one, but attempt to maintain our patients at 15 to 20 per cent of normal, for it has been our experience, as others also have reported,13 that clotting occasionally recurs when a patient's prothrombin time rises above 20 per cent. This is especially true early in the course of therapy.

After the control determination of prothrombin, which may be done at any time depending on the hour of admission, the blood for the prothrombin times was drawn at approximately 10:00 a.m. daily (except Sunday) and the determinations were completed by the laboratory within 2 hours. At a daily conference of the anticoagulant team, the appropriate dose for each patient was chosen. The prothrombin levels and daily dose of anticoagulant were recorded on a special sheet in the patient's chart and the drug was ordered to be administered at 3:00 p.m. in a single dose.

Estimations of the activity of the prothrombin complex were determined according to the Link-Shapiro modification of Quick's 1-stage method, except that Simplastin was used as the thromboplastin extract. We have found this substance to be quite stable and to yield uniform results from lot to lot. The prothrombin estimations were recorded both in seconds and as percentage of activity of a dried, stable, normal plasma standard. The above method is used routinely for the control of all prothrombin depressants in our hospital. All tests are performed by 1 of 3 experienced technicians; any questionable result is repeated.

RESULTS

We have analyzed the records of the first 100 patients treated with Sintrom and the previous 100 consecutive cases treated with Dicumarol. The only patients whose results were not included in each analysis were those in both groups who did not receive at least 10 days of maintenance therapy. We believe this is the minimum time necessary to establish an average maintenance dose with any oral anticoagulant.

In figure 1 the 2 groups are analyzed according to diagnoses and sex. On these bases the distribution of patients in the 2 groups was quite comparable.

Induction Therapy

We found early in the study, as have others,5, 7, 12, 14 that Sintrom will produce a therapeutic hypoprothrombinemia in virtually all patients in 48 hours or less. Therefore, in order to compare the rapidity of induction by Sintrom with other anticoagulants we have defined the induction phase as those 43 hours between the initial dose at 3:00 p.m. and the second prothrombin determination after therapy has been started.

Our usual induction doses were as follows: using Dicumarol alone we gave 300 mg. the first day and 200 mg. the second day. When using Tromexan in combination with Dicumarol to obtain more rapid induction, we gave 1200 mg. and 200 mg. respectively the first day, and 600 mg. and 200 mg. respectively on the second day. It should be emphasized that while these are the doses the majority of our patients received, they are by no means invariable. It is of great importance, as others have observed, to consider the clinical condition of the patient and the presence of concomitant disease when ordering any anticoagulant drug.

The most important factors we have found that may require a reduction in these average doses are congestive heart failure, hepatic disease, renal disease, marked malnutrition, and severe systemic illness.

There were 71 inductions with Sintrom for which prothrombin times were available at the end of 43 hours; of these, 67 patients or 94 per cent were in the therapeutic range by this time. Of 50 inductions with Tromexan and Dicumarol combined, 44 patients or 88 per cent were in the therapeutic range at 43 hours. In contrast, of 47 inductions with Dicumarol

![Fig. 1. Analysis of patients treated by Sintrom (solid) and Dicumarol (open) according to diagnoses and sex. Sintrom 70 males, 30 females; Dicumarol 68 males, 32 females.](image-url)
alone, only 14 or 30 per cent were within this range after 43 hours. This analysis shows the rapid action of Sintron and illustrates well the advantage of supplementing Dicumarol with Tromexan during the induction phase.

In order to ascertain the earliest time at which the usual induction doses of 28 and 18 mg. of Sintron would produce a therapeutic effect, 10 patients had prothrombin times done at 24, 30, 36, and 48 hours after administration of the first dose in addition to their control determination. These results are shown in figure 2. Thirty hours after the initial dose of Sintron was given, 7 of these 10 patients were within the therapeutic range and at the end of 36 hours all 10 had an adequate hypoprothrombinemia. If one considers the average times of these patients, as represented by the heavy line in the graph, it is evident that therapeutic prothrombin depression can be expected in most patients receiving these induction doses 30 hours after therapy has been initiated.

**Maintenance Therapy**

We have found as a general rule that the dose on the third day of Sintron therapy can safely be based on the prothrombin level. If the latter is 10 to 15 per cent of normal, 2 to 4 mg. are given; for 15 to 20 per cent of normal, 6 mg.; and if it is 20 to 30 per cent, 8 mg. are necessary. Thenceforth the appropriate dose on any day is based primarily on the depressant effect of the previous day's dose on the prothrombin time.

The average maintenance doses required to keep our patients in the therapeutic range and the average prothrombin percentage during maintenance therapy were determined for each group of 100 cases. The average daily Sintron dose was 5.9 mg., which maintained the prothrombin activity at an average of 18 per cent of normal. In the Dicumarol-treated group 78 mg. daily were required to maintain the prothrombin activity at an average of 21 per cent of normal. From these data it would seem that 2 mg. of Sintron is roughly equivalent in activity to 25 mg. of Dicumarol and we have found that this relationship is valid clinically, as mentioned previously. In figure 3 we have grouped the patients from each series according to this equivalence in dosage, and according to their average daily requirement of each anticoagulant. From this chart one can see that a normal distribution curve is approximated by each group. In addition, however, this graph suggests that there is a wider variation in the required daily dose from patient to patient with Sintron than with Dicumarol. The total at both extremes of average dosage requirement with Sintron (2 to 4 mg. and 10 to 12 mg.) was 29 patients. On the other hand, in the group receiving Dicumarol there were only 13 cases that required as little as 25 to 50 mg. or as much as 125 to 150 mg. for an average maintenance dose.

Our experience with Sintron represents 2,044 patient-days of maintenance therapy; of this total, our patients were in the therapeutic

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**Fig. 2.** The prothrombin depressant effect of Sintron in 10 patients from the usual induction doses, as determined by the prothrombin activity in per cent of normal (ordinate) 24, 30, 36, and 48 hours after initial dose.
range 91 per cent of the time. In the group treated with Dicumarol there were 2,289 patient-days of maintenance therapy and these patients were in the 10 to 30 per cent range for 87 per cent of this time. In figure 4 we have grouped the patients to compare the therapeutic control with Sintrom and Dicumarol. We consider that a patient’s anticoagulant therapy has not been well controlled unless at least 80 per cent of his prothrombin determinations fall within the therapeutic range. Thus it is significant that in the Sintrom-treated patients there were only 19 in the therapeutic range less than 80 per cent of the time, but with Dicumarol there were 34 in this group.

Recovery Phase

The rapidity of return toward normal prothrombin activity on cessation of therapy with Sintrom was not determined for all 100 patients treated with this drug, since it has been our policy for the past few years to “taper off” all anticoagulants rather than to stop them abruptly, in order to avoid a rebound phenomenon. There were, however, 24 of our patients that either through intent or through nursing

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**Fig. 3.** A comparison of the average maintenance dose distribution of Sintrom (solid) and Dicumarol (open), 100 cases each. A normal distribution curve is seen in both groups but a wider variation in dosage is seen in the Sintrom series.

**Fig. 4.** A comparison of the 2 groups of patients as to per cent of time within the therapeutic range (10 to 30 per cent of normal). Sintrom, solid; Dicumarol, open bar.
TABLE 1.—Return of Prothrombin Activity Toward Normal in Eleven Patients after Intentionally Omitting One Daily Dose Because of a Low Prothrombin Activity

<table>
<thead>
<tr>
<th>Prothrombin per cent on day Sintrom dose not ordered</th>
<th>Prothrombin per cent 24 hours later</th>
<th>Days of therapy prior to omission of Sintrom dose</th>
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TABLE 2.—Return of Prothrombin Activity Toward Normal in Fourteen Patients after One Daily Dose Was Omitted through Error

<table>
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<th>Prothrombin per cent on day Sintrom dose omitted</th>
<th>Prothrombin per cent 24 hours later</th>
<th>Days of therapy prior to omission of Sintrom dose</th>
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Complications

Three patients who were being treated with Sintrom for acute myocardial infarctions had gross hematuria and received vitamin K$_1$ intravenously. The first patient, a 54-year-old woman, developed gross hematuria and ecchymoses on the thirty-seventh day of therapy, when her prothrombin activity fell to 3 per cent of normal. Thirty-five milligrams of vitamin K$_1$ were given intravenously and within 2 hours her prothrombin activity was 12 per cent; 20 hours later it was 67 per cent. The second patient, a 68-year-old man, developed gross hematuria on the eighteenth day of therapy at a prothrombin level of 7 per cent. Two hours after the administration of 10 mg. of vitamin K$_1$ intravenously, his prothrombin time was 19 per cent and 20 hours later it was 47 per cent of normal. The third patient, a 68-year-old man, developed gross hematuria coincident with a prothrombin level of 5 per cent on the twenty-second day of therapy. Two hours after he had received 10 mg. of vitamin K$_1$ intravenously, his prothrombin level was 36 per cent and after 20 hours it was 72 per cent of normal. In all 3 patients the hematuria had ceased within 4 to 6 hours after the administration of the vitamin K$_1$.

Discussion

A new anticoagulant may be evaluated by determining its clinical characteristics and comparing them with those drugs available for clinical use and with those of an “ideal anticoagulant,” as outlined earlier in this paper. Although no drug presently available meets all these requirements, we believe that Sintrom has certain qualities that make it superior to many of the other drugs now in common usage.

Sintrom induces a therapeutic hypoprothrombinemia in most patients 36 hours after the initial dose is given when the induction schedules outlined are followed. This compares favorably with the rapidity of action of Tromexan. When we compared our results with those obtained in a group of 89 patients who received only Tromexan, we find that a slightly higher percentage of our Sintrom-treated patients were within the therapeutic
range (94 per cent vs. 80 per cent) 43 hours after the initial dose was given. However, Tromexan induced a therapeutic level in 27 per cent of these 89 patients by the end of 24 hours. Other workers\cite{5,7,14} have stated that a therapeutic prothrombin level could be obtained by the end of 24 hours with Sintrom with smaller induction dose than we used. We have been unable to duplicate their results; in fact, when we reviewed the records of all patients who received our first induction dose of 28 mg., we found only 1 patient who had a therapeutic prothrombin level by the end of 24 hours. To verify this further, we gave 10 patients without thromboembolic disorders a single 28 mg. dose of Sintrom and determined their prothrombin times at intervals of 6 hours for 48 hours. The maximal depressant effect was seen in 24 hours, but the lowest level any patient reached by that time was 40 per cent of normal. In contrast are the results in the 10 patients who received 18 mg. of Sintrom 24 hours after the first dose and who also had frequent prothrombin determinations (fig. 2). All these patients had a therapeutic prothrombin level 36 hours after therapy was begun. Thus 1 loading dose of Sintrom is inadequate but if the 2 recommended induction doses are given on successive days, a rapid hypoprothrombinemia will be obtained. With the exception of those relatively few patients who had congestive heart failure, hepatic disease, renal disease, malnutrition, or a severe systemic illness, all of our patients received the 2 induction doses. Other workers recommend somewhat smaller\cite{12} and larger doses.\cite{2,7,14} On this regimen we have had no patient whose prothrombin activity was less than 10 per cent at the end of the induction phase. When the schedule for the third day’s dose is followed, the prothrombin level is easily modified if necessary, and subsequent maintenance doses are determined by the effect of the previous day’s dose of Sintrom. This association is primarily a reflection of the relatively short duration of action of Sintrom, which we believe contributes greatly to the ease of control of therapy with this drug. We have not observed the rapid fluctuations in prothrombin levels commonly seen with Tromexan therapy, which may necessitate the use of divided daily doses for smooth control. Aeppli and Rubeli\cite{12} have found that immediately after the optimum effect of Tromexan has occurred, the “coagulation valence” begins to rise again. In contrast they found that the maximum anticoagulant effect of Sintrom occurs as rapidly as with Tromexan but remains constant for 15 to 20 hours, after which there is a rapid rise in the prothrombin activity. On the other hand, the effect of Dicumarol usually does not begin until 24 hours after a given dose and may continue for as long as 72 hours, or even longer after a prolonged period of therapy. Another recently introduced anticoagulant (Dipaxin) is reported to produce a therapeutic prothrombin level in 48 to 60 hours and to require a recovery period of 15 to 20 days after the drug is withdrawn.\cite{16, 17} The long recovery periods of Dicumarol and Dipaxin are claimed to be an advantage, for the omission of a single dose does not interrupt the continuity of therapeutic control and a patient’s prothrombin time returns more slowly toward normal at the termination of therapy. We believe, however, that any anticoagulant with a long duration of effect has certain disadvantages that often outweigh these apparent advantages. 1. In the event of minor hemorrhagic complications or excessive hypoprothrombinemia, the anticoagulant effect can be counteracted rapidly only by the administration of vitamin K. While this is effective, the use of vitamin K is often associated with a “rebound hypercoagulability” that may result in thromboembolic complications. 2. If surgery or other procedures become necessary, even if they can be deferred for 24 hours, the use of vitamin K is nearly always necessary. 3. When vitamin K is used to reverse the effects of a long-acting anticoagulant, relatively large doses are necessary and the patient is usually resistant to anticoagulants for several days thereafter. This disadvantage, when continuation of therapy is advisable, has not been observed with Sintrom.

Figure 3 shows a wider variation in maintenance dose with Sintrom than with Dicu-
marol from patient to patient. However, once the daily requirement of a patient has been established and transient anticoagulant sensitizing factors have been eliminated, the dose for an individual patient varies relatively little.

We believe that our results with Sintron are quite good and attribute this in part to our "team system" of anticoagulant management. A major factor is, however, the ease of control with this drug. Its rapid onset of action and 15- to 20-hour duration of effect are great advantages in its clinical use; its position in the "anticoagulant spectrum" makes it worthy of consideration for general clinical use.

SUMMARY

We have presented a report on our experience in treating patients with a new coumarin anticoagulant, Sintron, and have compared it with Dicumarol and Tromexan. It seems to offer certain advantages over these drugs when they are used alone: (1) it will induce a therapeutic prothrombin level in most patients 36 hours after the initial dose, (2) when given in a single daily dose, a therapeutic effect is easily maintained, (3) it is rapidly excreted and the elimination of 1 dose usually results in a prompt return of the prothrombin time toward normal, (4) vitamin K₁ in relatively small dosage counteracts its effect within a few hours, (5) the dosage is relatively constant in a given patient but, as with all anticoagulants, may vary with changes in the clinical condition of the patient—like other oral anticoagulant drugs, the dose required to maintain a therapeutic level varies greatly from patient to patient, (6) we have found this drug well tolerated when administered orally, (7) a limited experience with Sintron suggests that it is a more nearly ideal anticoagulant than any of the commonly used coumarin or indanedione derivatives. Further study under more varied conditions is indicated.

SUMARIO IN INTERLINGUA

Nos ha presente un reporto de nostre experientias in le tractamento de patientes con le nove anticoagulante coumarinic Sintron e ha comparerlo con Dicumarol e Tromexan. Sintron pare haber certe avantages super le altere mentionate drogas quando illos es usate sol. (1) Sintron induce un nivello therapeutic de prothrombina in le majoritate del patientes 36 horas post le dose initial. (2) Le efecto therapeutic de Sintron es facile a mantenir per administrar un sol dose per die. (3) Sintron es excernita rapidemente, e le elimination de 1 dose resulta usualmente in le prompte retorno del tempore prothrombinico verso le norma. (4) Vitamina K₁ in relativemente parve doses neutralisa le efecto de Sintron intra pauc horas. (5) Le dosage de Sintron es relativemente constante in le mesme patiente sed pote variar (como le dosage de omne anticoagulantes) in le presentia de alterationes del condition clinic del patiente. Le dosage de Sintron (como le dosage de altere anticoagulantes oral) que es requirite pro mantenir un nivello therapeutic varia grandemente ab un patiente al altere. (6) Nos ha trovate que Sintron es ben tolerate in administrationes oral. (7) Nostre experientias con Sintron es limitate sed illos suggere che iste droga satisfache le criterios del anticoagulante ideal a plus alte grados que le derivatos de coumarina e indanedione de uso commun. Studios additional sub varie condiziones es indicate.

REFERENCES


Subsequently, in the celebrated Commentaries upon which our grandfathers in the profession were educated, Heberden gave a fuller account of his experience with the disease. The name which he adopted can not be regarded as altogether satisfactory, since it was already in use in designating affections of the throat, with which its literal meaning—a strangling—is much more in harmony. In one sense, however, the term is fairly appropriate, since, as noted by Gairdner, the words anxiety and anguish, expressive of two of the most prominent features of the disease, have a derivation from the same Greek word as angina.—William Osler, M.D. Angina Pectoris and Allied States. 1897.