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CLINICAL EXPERIENCE WITH A NEW ANTICOAGULANT, SINTROM (G 23350)

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As indicated by numerous publications[1,2] over the last 16 years, the use of coumarin drugs in anticoagulant therapy has been thoroughly investigated. However, the search for a so-called 'ideal' anticoagulant drug has continued. Such a 'prothrombin' depressant should meet the following requirements:[3]

1. It should act rapidly in lowering the prothrombin index to a therapeutic level.
2. Single daily doses should suffice to prevent fluctuations of the prothrombin index.
3. It should be metabolized or excreted quickly enough to allow a rapid return to normal of the prothrombin index after cessation of therapy.
4. A suitable pharmacological antagonist should rapidly counteract its effect in case of emergency.
5. The doses should be relatively constant in a given patient and from patient to patient.
6. Oral administration should be effective.
7. It must be non-toxic and well tolerated in therapeutic dosages.
8. It should be satisfactory for use as an ambulatory drug.

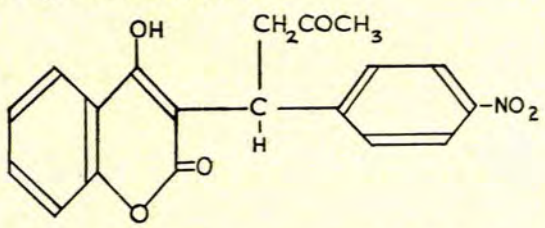
In addition, the cost of the drug should not be prohibitive.

At present, no drug available meets with all these requirements, but a new coumarin derivative, nitro-phenyl-acetyl-ethyl-4-hydroxycoumarin, commercially known as Sintrom* (G 23350), which was synthesized by Stoll and Litvan,[4] is stated to approach the 'ideal' prothrombin depressant more closely than many of the other anticoagulant drugs.[3]

Sintrom has to date not been used in South Africa and the purpose of this paper is to report our experiences with the use of this drug.

Chemical Properties (as determined by Montigel and Pulver[6])

Sintrom is a 3-(α-[4′-nitrophenyl]-β-acetyl-ethyl)-4-hydroxy-coumarin. The chemical formula is $C_{19}H_{15}NO_6$. It has the following structural formula:



It is a crystalline light-brown powder, which is almost tasteless and odourless. The molecular weight is 353 and the melting point 191-192°C. It is slightly soluble in organic solvents and in water, and becomes increasingly soluble in water as the pH is raised. It is a weak acid and is chemically stable. With alkalis it forms water-soluble salts.

Mode of Action

The mode of action and metabolism of sintrom have been thoroughly investigated by European[5,6] and American[3,7,8] workers. As with other coumarin derivatives, it causes a depression of factor VII (stable factor or pro-convertin) activity and to a lesser extent of prothrombin, early in the course of the treatment.[9] Both are equally affected after several weeks of treatment.[10] Factor V (labile factor or pro-accelerin) and antihaemophilic globulin are not influenced.[6,16] It probably also acts as an antagonist of vitamin K.[8] Sintrom, like other coumarins, is active only *in vivo* and not *in vitro*.[17]

Sintrom rapidly disappears from the body. It is excreted by the kidneys in an unaltered state, in contradistinction to other coumarins such as tromexan, which is converted to an inactive tromexan acid.[6] Degradation products of sintrom are found only in small quantities.[6]

To investigate the distribution of sintrom and dicoumarol in the body, Montigel and Pulver[6] administered 100 mg./kg. of sintrom or 20 mg./kg. of dicoumarol orally to rabbits each day, over a period of 4-6 days. The rabbits were killed 8 hours after the last dose and the amount of drug in each organ estimated. They found that dicoumarol accumulated not only in the blood but also in the tissues; the concentration in the liver was, on an average, 1/3rd of that in the blood. In contrast, sintrom was found in larger amounts in the liver than in the blood. The other organs, e.g. brain, heart, spleen, muscle and fatty tissues, contained only relatively small amounts of dicoumarol (0·5 - 2·3 mg.%) and sintrom (0·2 - 1·2 mg.%)

Montigel and Pulver found that if they injected rabbits intravenously with sintrom, tromexan or dicoumarol using doses of 5 mg./kg., the blood concentration fell from 3·5 mg.% to 0·2 mg.% in 2 hours with tromexan; with sintrom it fell from 3·5 mg.% to 0·7 mg.% in the same time. After dicoumarol, however, the blood concentration fell much more slowly, and an initial level of 4·8 mg.% reached only

* Geigy Pharmaceuticals, Basle, kindly supplied Sintrom for use in this investigation.

2·5 mg.% after 2 hours and was still 2·0 mg.% after 6 hours.

Pratt[7] found that sintrom had a very low toxicity. Rabbits withstood dosages of 0·5 - 5 mg./kg. for 2 months without symptoms. Animals whose prothrombin level was maintained at 20-40% for 9-12 weeks, showed no post-mortem internal bleeding or toxic liver damage. The haemoglobin concentration and blood picture of these animals remained unchanged.

In an animal experiment to show the lethal dose of various antithrombic substances, Montigel and Pulver[6] found that 1,470 mg./kg. of sintrom was lethal to a mouse, as opposed to 840 mg./kg. of tromexan.

Jürgens[5] claims that the action of sintrom begins within 12 hours after administration of a single dose, and reaches its maximum effect after about 2 days. It remains at this level for a brief period, followed within the next 2-3 days by a relatively rapid complete normalization.

Aeppli and Rubeli[14] state that the maximum anticoagulant effect of sintrom occurs as rapidly as with tromexan, but remains constant for 15-20 hours, after which the prothrombin level rises rapidly.

To assign sintrom a place in the anticoagulant drug 'spectrum', it has been suggested that it is intermediate in action between tromexan and dicoumarol.[6,10,20] Tromexan has a short transient action and a relatively low activity and toxicity; dicoumarol acts for a longer time and has a higher activity and relatively high toxicity.[6]

MATERIALS AND METHODS

Eighteen patients (Table I) having various thrombophlebitic disorders of the lower limbs were studied over a period of from 16 to 241 days. The total patient-days were 1,128. All the patients were ambulatory after the initial pain was relieved.

Venous blood samples were collected in the morning and the prothrombin indices estimated within 2-3 hours of collection.

The prothrombin index was determined according to the method of Stein.[11] The results were expressed as 'prothrombin index' (PI), which is calculated by dividing the prothrombin time of normal plasma (estimated daily) by that of the patient's plasma and expressing the result as a percentage.*

Once the maintenance dose had been established, the prothrombin index was estimated once or twice weekly (usually only once a week). We should have preferred to perform the PI estimation more frequently, but this was impracticable, for in many instances the patients lived as far afield as 40 miles.

Clinical examinations were carried out on every patient before and during the investigation. Particular attention was paid to the duration of bleeding from the venepuncture site, when blood had been withdrawn for PI estimations.

RESULTS AND DISCUSSION

Administration of Dosage

Sintrom is supplied in 4 mg. tablets. Neill *et al*[3] found that 2 mg. of sintrom are roughly equivalent to 25 mg. of dicoumarol (i.e., one 4 mg. tablet of sintrom = 50 mg. of dicoumarol) by using the following method: 35 patients were initially treated with dicoumarol and when the average maintenace dose of each patient had been established, sintrom was substituted to maintain an equivalence in dosage between these two drugs.

The mean *induction dose* for sintrom in this series was 34·4 mg. (8·6 tablets). The range was from 6 to 12 tablets, given in either divided or single doses. Neill *et al.*[3] used 2 induction doses on successive days and Menéndez *et al.*[8] recommended an induction dose of 32 mg. given in a single dose. We did not find that either the divided or single induction dose method had any advantage over the other. Jürgens[5] found that the rapidity of onset of action is practically independent of whether sintrom is given at one time or in fractionated doses.

In an attempt to verify these conclusions further, we performed the following experiment: 2 normal subjects

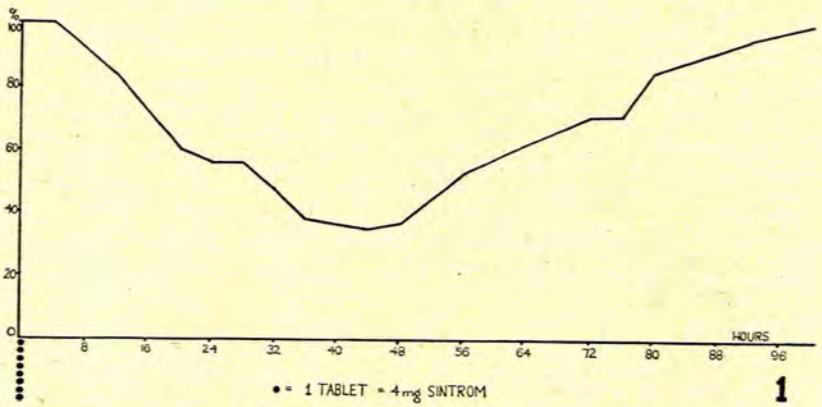


Fig. 1. Single dose of sintrom administered to normal subject A.

(A and B) were given single and divided doses respectively. A, weighing 150 lb., received 32 mg. in one dose. B, weighing 135 lb., received 16 mg. and, 24 hours later, another 12 mg. PI estimations were performed at 4 hourly intervals, whenever possible, by the finger-prick method of Stein and Wallace.[19] A decided fall in the prothrombin index was obvious 12 hours after the induction dose in both cases. The lowest point was reached in 44 and 36 hours respectively. The prothrombin index remained fairly constant for a short while, after which

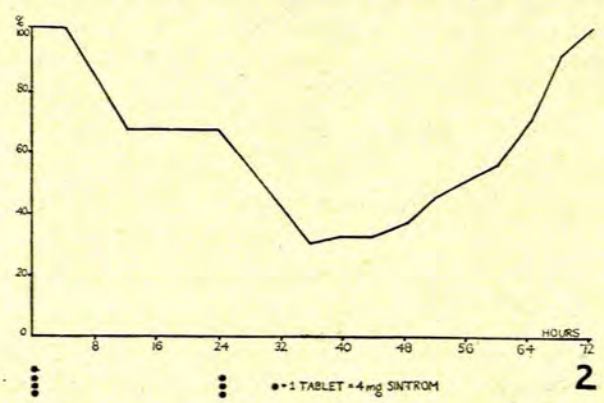


Fig. 2. Divided dose of sintrom administered to normal subject B.

* These results can be converted to prothrombin concentration or coagulation valency by means of a calibration curve.[11]

TABLE I. SUMMARY OF 18 CASES TREATED WITH SINTROM

Sex	Age	Weight (lb.)	Disease	No. of days on treatment	Dose: Induction (a) (tablets)	Dose: Average maintenance (mg.)	% of days within therapeutic range (30-70%)
Male	28	150	Acute deep-vein thrombophlebitis in a post-phlebitic leg	129	8	5·0	68%
Male	34	200	Deep-vein thrombophlebitis in a post-phlebitic leg	20	7	3·7	92%
Female	44	155	Deep-vein thrombophlebitis	50	7	5·0	41%
Female	24	130	Deep-vein thrombophlebitis	28	7	7·0	43%
Female	39	155	Deep-vein thrombophlebitis	51	6, 4	5·6	62%
Female	40	145	Deep-vein thrombophlebitis	92	2, 2, 2	5·4	21% (d)
Male	65	160	Deep-vein thrombophlebitis plus infectious mononucleosis	59	4, 3	2·5	89%
Female	21	105	Deep-vein thrombophlebitis plus infectious mononucleosis	55	heparin	2·5	54%
Female	42	180	Recurrence of deep-vein thrombophlebitis in a post-phlebitic leg.	96	4, 4	3·9	89%
Female	47	162	Post-operative (radical for varicose veins) thrombophlebitis	51	dicoumarol (b)	3·8	77%
Male	44	160	Post-operative (radical for varicose veins) thrombophlebitis	30	8	4·3	100%
Female	62	200	Acute deep and superficial thrombophlebitis in a post-phlebitic leg	54	8, 4	4·9	71%
Female	70	95	Acute superficial thrombophlebitis	54	7, 4	4·1	95%
Female	56	186	Superficial thrombophlebitis.	17	8, 4	5·8	85%
Female	37	280	Superficial thrombophlebitis	16	7	4·0	81%
Male	52	150	Superficial thrombophlebitis	36	heparin	5·4	29% (d)
Male	47	200	Extensive thrombophlebitis migrans.	241	7, 4 (c)	4·0	86%
Male	42	170	Idiopathic deep-vein thrombophlebitis plus arterial spasm.	49	8	3·8	100%

(a) Where 2 (or 3) figures are given, the induction was by means of doses given on 2 (or 3) successive days.
(b) On dicoumarol treatment initially.
(c) On dicoumarol treatment initially but allowed to return to normal before sintrom administration.
(d) Patients who were not cooperative.

TABLE II. PHARMACOLOGICAL PROPERTIES

Chemical Name	Name of Drug	Time required to reach therapeutic levels (hours)	Time required to return to normal after single dose (days)	Dosage: Initial (mg.)	Dosage: Maintenance (mg.)	Side-effects
3, 3'-methylene bis(4-hydroxycoumarin)	Dicoumarol Dicoumarin	48-72	5-6	200-300	25 or less—100	Nausea, depression, nightmares
bis-3,3'-(4-oxycoumarinyl)-ethyl-acetate (B.O.E.A.)	Tromexan	18-36	1-2	1,200-1,500	150-900	Unknown in our experience
3-[-(4'-nitrophenyl)-β-acetyl-ethyl]-4-hydroxycoumarin	Sintrom	24-72	2-3	32	2-7	No side-effects
3-(α-acetonyl benzyl)-4-hydroxycoumarin	Sodium Warfarin (Coumadin)	24-36	5-6	50-75	5-10	Unknown in our experience
phenyl-indanedione	Dindevan Indema	24-36	2-3	150-300	25-100	Gastro-intestinal upset and nausea
2-(diphenyl-acetyl)indane- 1:3-dione	Dipaxin	24-72	up to 6	20-30	2-5	Unknown in our experience
2-diphenyl-acetyl-1,3-indanedione	Didandin (Diphenadione)	48-72	15-20	20-30	5-10	Unknown in our experience

there was a rapid return to normal (in 2 and 1 days respectively). (Figs. 1 and 2.)

Sintrom induces a therapeutic hypoprothrombinaemia in most patients 36 hours after the initial dose is given.[3] Neill *et al.*[3] found that 94% of their patients were in the therapeutic range by the end of 43 hours after the induction dose. We found that 77% of our patients were within the therapeutic range (PI 30-70%, corresponding to a coagulation valency of 10-42%) in 24 hours. All the patients except one who did not come for his PI estimation on the appointed day) were therapeutically controlled in 48 hours.

The average *maintenance dosage* in our series varied from 2·5 to 7 mg. (mean=4·5 mg.) daily as indicated by the prothrombin index. Relatively small changes in the dosage rapidly influenced the prothrombin index. The doses were adjusted as follows:

Prothrombin Index	*Daily Dose of Sintrom*
30-40%	2 mg. (=½ tablet)
40-55%	4 mg. (=1 tablet)
55-70%	8 mg. (=2 tablets)
over 80%	10-12 mg. (=2½-3 tablets)

The maintenance doses as well as the initial doses were administered once daily, reducing thereby the cost and inconvenience of the treatment. This is an advantage sintrom has over other quick-acting coumarin derivatives, which must be given several times a day to obtain a constant prothrombin index.

The maintenance dose, once established, did not vary greatly, although it was sometimes found that a patient who had been well controlled for several weeks on 1 tablet daily, suddenly required more (i.e. 2 tablets daily). The daily dosages did not usually differ greatly from patient to patient (Table I), although Neill *et al.*[3] found that there was a wide variation from patient to patient in the maintenance doses. Out of a total of 100 patients they found that 29 required as little as 2-4 mg. daily or as much as 10-12 mg. daily.

The effects produced by sintrom, as with all anticoagulants of the coumarin type, can be reversed by the administration of vitamin K_1.[8,3] Vitamin K_1 need only be used in cases of severe haemorrhage, because it acts very rapidly as an antidote to sintrom.[8] Neill had 2 patients whose prothrombin activities were below 10%. Twenty hours after intravenous injections of vitamin K_1, the levels rose by 64% and 40% respectively.[3] In mild haemorrhages, it is sufficient merely to interrupt the dosage in order to stop the bleeding.[6] This may be regarded as a practical advantage, because the action of vitamin K_1 complicates subsequent therapy with

coumarin derivatives.[6] Should surgery or a tooth extraction become necessary during therapy, it is a simple matter to allow the prothrombin index to return to normal within a short while (2-3 days) by cessation of therapy. Neill *et al.*[3] found that a patient whose prothrombin index had been depressed to a hazardous level could be brought to a safe therapeutic level by eliminating one dose.

Side-effects. Sintrom is well-tolerated orally and has no side-effects in the form of nausea, anorexia, headache or vertigo, and has a low toxicity. In their animal experiments Montigel and Pulver[6] found that the lethal dose of sintrom administered to mice is much higher even than that of tromexan. Two of our patients, who were on dicoumarol therapy initially and subsequently continued with sintrom, were very favourably impressed by the sense of well-being they experienced on the change of drug. Some of the other anticoagulant drugs, dicoumarol especially, may cause severe mental depression, irritability, and sleeping irregularities in the form of nightmares. Sintrom, so far, has produced no such side-effects.

Some of the pharmacological properties of sintrom are compared with those of other coumarin and indanedione anticoagulants in Table II.

Contra-indications. As with other coumarin derivatives, sintrom should not be used in the presence of haemorrhagic diathesis, severe parenchymal liver damage, kidney insufficiency, ulceration of the digestive tract, or pregnancy, and during neurosurgical interventions. Care should be exercised if sintrom is administered together with other drugs, because salicylates[18] and PAS, for example, sometimes diminish the prothrombin index, while digitalin and strophantin increase it.[16]

Clinical Management of Cases

The patients investigated in this series varied in age from 21 to 70 years and suffered from thrombophlebitis of one type or another in the lower limbs:

1. Acute deep-vein thrombophlebitis: femoral, iliofemoral and those presenting in the deep venous plexus of the calf.
2. Superficial thrombophlebitis: (*a*) due to trauma, (*b*) secondary to varicose veins, (*c*) idiopathic superficial thrombophlebitis migrans, and (*d*) localized superficial idiopathic thrombophlebitis.
3. Recurrent acute thrombophlebitis in a post-phlebitic limb.

It is now our custom to use anticoagulant therapy in all cases of thrombophlebitis—superficial and deep. The reason for this is that, although thrombo-embolic phenomena are commoner following deep thrombophlebitis, cases of thrombo-embolism following superficial thrombophlebitis have been reported.[15] In the experience of one of us (I.N.) two such embolic phenomena resulted from a superficial thrombophlebitis before the use of routine anticoagulant therapy. As soon as the acute pain had subsided, the patients were made ambulatory and supplied with efficient supportive bandaging. Elevation of the bed when sleeping and brisk walking rather than standing were insisted upon, as well as elevation of the leg when sitting. Smoking was not allowed and the obese patient was ordered to reduce weight.

Anticoagulant therapy was usually recommended for at least 8 weeks after the pain had subsided, because of the high incidence of recurrences with insufficient therapy.

Haemorrhages, nose bleeds and macroscopic blood in the urine did not occur, although prolongation of the menstrual bleeding occurred in some of the female patients.

Results

Although most workers consider the therapeutic range for the PI to be between 30 and 50% of normal, corresponding to a coagulation valency of 10-21%,[12] others[13] have aimed at ranges of 50-70% (coagulation valency 21-42%). In this study we have aimed at maintaining the prothrombin index between 30 and 70%. We realize that there may be some objection to this wide range, but since all our patients were ambulatory we feel we were justified. Clinically, we have noticed that there is a marked improvement in the patients' condition even when the PI is 70%. Although

TABLE III. CONTROL OF PROTHROMBIN INDEX

% of Days during which PI between 30-70%	*% of patients*
75-100	56
over 60	72

the figures shown in Table III do not seem to reflect a very good degree of control of the prothrombin index, it should be emphasized that, whereas in practice one is satisfied if the prothrombin index is slightly below or above the therapeutic range, strict interpretation of the results has been employed for the purpose of investigating the action of sintrom. If a patient's prothrombin index was immediately below 30% or immediately above 70%, it was regarded as being out of therapeutic control. Also, some of the patients in this series were difficult to control because of frank or suspected lack of cooperation and because PI estimations could not be performed more frequently than once a week. However, as it was our intention to show that sintrom can be given with safety to the ambulatory patient who is not under medical supervision for a large part of his or her treatment, it was deemed expedient to include these in this report.

Sintrom does not accumulate in the body[6] and the toxicity of the drug is so low that the effects of overstepping the prescribed dosage would not be disastrous. A week's supply of tablets is usually issued to the patient.

In all cases we found that the drug was well tolerated and patients did not suffer from any side-effects. There was no recurrence of thrombophlebitic disorders, or of complicating thrombo-embolic phenomena during therapy in the present series. No case of haemorrhage requiring cessation of

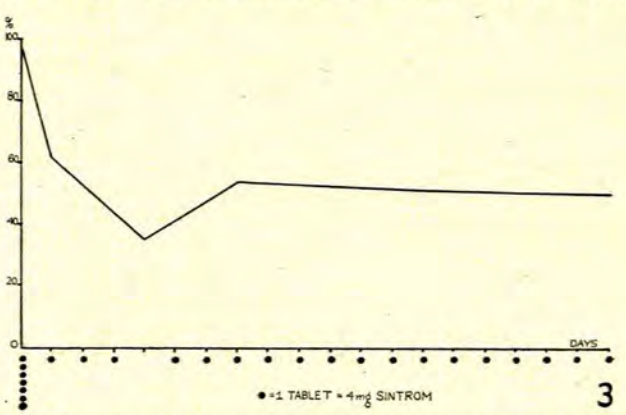


Fig. 3. Single induction dose of sintrom administered to patient.

therapy or the administration of vitamin K_1 occurred. Menéndez *et al.*[8] reported that vitamin K_1 in 50 mg.-intravenous doses is effective as an antidote to any bleeding that may occur.

In the limited study, we found that neither the single nor divided induction dose methods seemed to have any advantage over the other. Figs. 3 and 4 show the degree of control that can be achieved in the ambulatory patient with single and divided induction doses respectively.

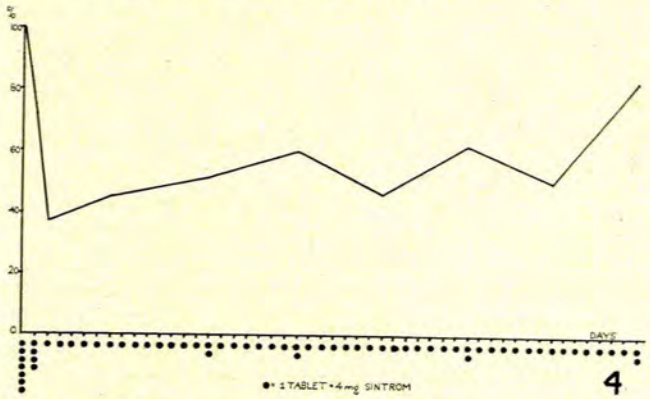


Fig. 4. Divided induction dose of sintrom administered to patient.

It is also possible to change from dicoumarol to sintrom without any difficulty, as can be seen from Fig. 5.

We feel that a further study is necessary, and we hope to present results on hospitalized patients treated with sintrom in a forthcoming publication.

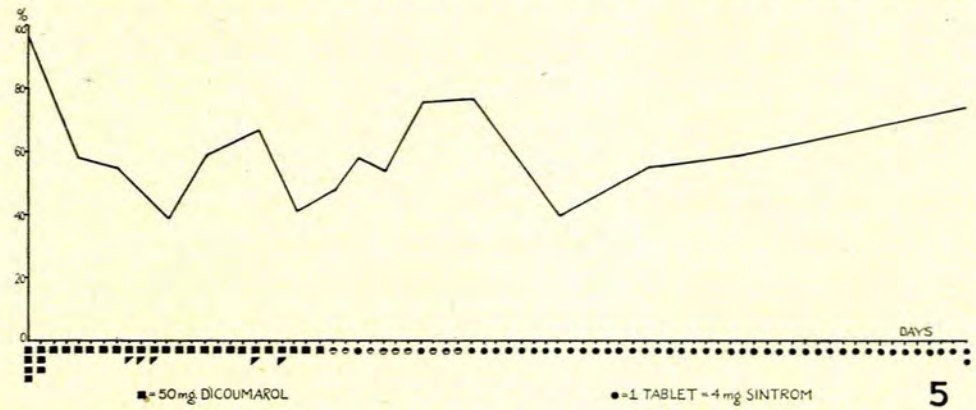


Fig. 5. Patient's therapy initially dicoumarol, subsequently changed to sintrom.

SUMMARY

We have presented a report on our experience in treating 18 ambulatory patients suffering from thrombophlebitis with a new coumarin anticoagulant drug called Sintrom.

1. The chemical and pharmacological properties of the drug are briefly described.

2. Sintrom induces a therapeutic prothrombin level (index 30-70% of normal, corresponding to a coagulation valency of 10-42%) in most patients 24 hours after the initial dose, which is given as a single or divided dose of 24-48 mg.

3. Maintenance doses are given once daily and vary from 2-7 mg. per day.

4. Estimations of the prothrombin index were usually performed once or twice a week, but this is not ideal.

5. No haemorrhages or thrombo-embolic complications occurred.

6. No undesirable side-effects were caused by the drug.

7. After cessation of therapy there is a rapid return to normal (1-2 days in 2 normal subjects).

8. Tentatively, it may be concluded that sintrom is a satisfactory anticoagulant for use in the acute and ambulatory case of thrombophlebitis.

We wish to express our sincere thanks to Dr. B. A. Bradlow and Dr. D. Mendelsohn for their kind suggestions and criticisms.

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