Some Observations on the Coagulation Defect During Treatment with the Anticoagulant "Sintrom"

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In an earlier publication (7) we reported our clinical experiences with the anticoagulant "Sintrom", a coumarin derivative. The investigation described in the following pages deals especially with the problem of the mutual relationship between the decrease of prothrombin and of factor VII. Also a simple test is described to demonstrate an important difference between the coagulation defect in hepatitis and that on administration of Sintrom.

Methods

PT: coagulation time of oxalate plasma after addition of tissue thromboplastin (a commercial preparation of the Amsterdamsche Chininefabriek Ltd., the composition of which is a manufacturing secret not made known by the factory) and calcium-chloride solution (1/40 M). For normal plasma a coagulation time is found varying between 14 and 16 seconds (usually 15 seconds). This coagulation time is converted into a percentage by means of a dilution series of normal plasma in isotonic saline solution. The activity of the thromboplastin solution should be checked on normal plasma every day.

Factor VII: "one stage" method, in which the reagent of the Behringwerke is used (6). In fact the combined activity of F VII and Stuart Factor is measured. Here also the conversion into a percentage is done by means of a dilution series.

Prothrombin: "area method" according to Biggs and Douglas (1), this is a "two stage" method.

Thrombin generation test: we start with 0.5 ml. oxalate plasma, to which are added equal volumes of isotonic saline solution and calcium chloride solution. We further follow the directions of Macfarlane and Biggs (4).

Thrombin time: the coagulation time of oxalate plasma after addition of thrombin (preparation of the Blood Transfusion Service of Amsterdam). The coagulation time obtained with a given thrombin solution is 10—11 seconds for normal plasma (usually 10 seconds). The activity of the thrombin solution should be checked daily.

Results

We determined factor VII, prothrombin and PT of 210 plasma samples obtained from Sintrom-treated cases. The PT values found were arranged in

10 groups, namely < 10%, 10—19%, 20—29% . . . . etc. We calculated the average of the corresponding values of the two factors mentioned. The following table shows the results:

Table 1

PT	Factor VII	Prothrombin
%	%	%
< 10	20	58
10—19	23	65
20—29	30	74
30—39	39	79
40—49	45	82
50—59	60	88
60—69	62	84
70—79	79	89
80—89	87	90
90—100	90	91

It appears that a clear fall of prothrombin activity is only observed at factor VII values below 30%. In view of the greatly reduced activity of factor VII after administration of Sintrom and the much less marked disturbance of the prothrombin, one might suppose that properly speaking the action of the anticoagulant is completely based on the causation of a 'hypo-convertinaemia' without important 'hypo-prothrombinaemia'. When this is true, it must be possible to correct the defect with normal serum: serum possesses a strong factor VII activity but hardly any prothrombin activity. Haemophilia is attended by a decreased prothrombin consumption in the serum; haemophilic serum is therefore a source both of factor VII and of prothrombin (our method of determination yields a factor VII activity of haemophilic serum which is not lower than that of normal serum, while the prothrombin activity is considerably greater).

We studied the correcting influence of normal and haemophilic serum with regard to three different aspects of the coagulation defect caused by Sintrom, viz.: (1) the PT, (2) the 'two-stage' prothrombin determination and (3) the thrombin generation test.

In the case of the PT a serum dilution of 1 : 5 was used, in the other tests, however, undiluted serum. The control values were obtained by adding to the reaction mixture an equal amount of isotonic saline solution instead of serum. The thrombin yield in the thrombin generation test was calculated according to the principle of the 'area method'. We chose patients who showed a marked fall of the prothrombin level on the day of the experiment.

Table 2

	PT (20 cases) seconds	%	'two-stage' (10 cases) %	Thrombin generation test (6 cases) %
Control	15 (14—16)	100	100	100
Patients	32 (21—49)	23	40 (30—50)	22 (10—28)
Idem with normal serum	15 (13.5—17.5)	100	54 (44—71)	32.5 (22—53)
Idem with haemophilic serum	14 (12.5—15.5)	117	73 (61—100)	55,2 (41—97)

These figures show that, although the PT can be completely corrected by an agent containing factor VII but little or no prothrombin, the coagulation defect is certainly not absolutely abolished in this way. The 'two-stage' determination and the thrombin generation remain disturbed; the correction of these tests becomes better the more prothrombin is present in the correcting agent (fig. 1).

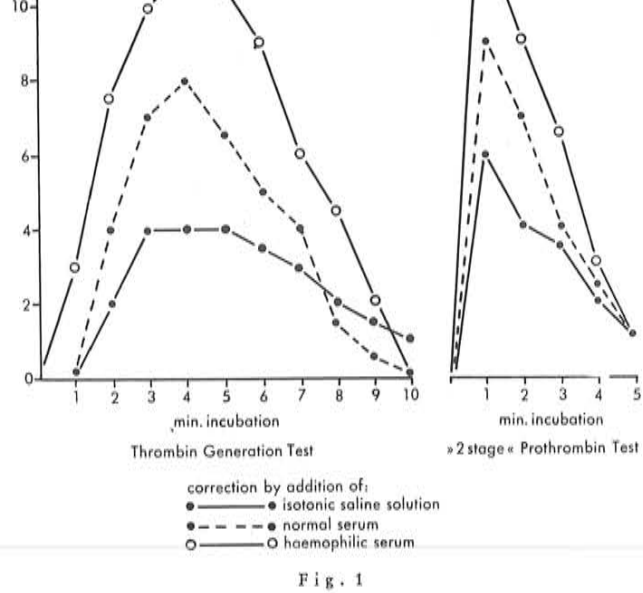

Fig. 1

In *hepatitis* a coagulation defect is often found, consisting of a prolongation of PT and heparin tolerance time, reduction of activity of factor VII and prothrombin, and also a disturbance of the thromboplastin generation test when

patient serum and normal $BaSO_4$ plasma are used. In cases with a favourable course the activity of factors V and VIII (A.H.G.) is usually not disturbed. In these cases the defect therefore shows a striking resemblance with the disturbance caused by Sintrom and other coumarin derivatives.

In none of the Sintrom-treated cases examined by us was the *thrombin time* markedly longer. For PT-values below 30% we found a prolongation of some seconds; the highest value of the thrombin time was 14 sec. (control 10 sec.). In cases of hepatitis the thrombin time was however always clearly prolonged; this is possibly due to the presence of a heparin-like antithrombin ("antithrombine immédiate") in the blood of sufferers from hepatitis. Marx calls the prolongation of the thrombin time a "general indicator" of hepatic diseases (5). The marked difference between the behaviour of the thrombin time on administration of Sintrom or in hepatitis is illustrated by fig. 2 (averages of 101 determinations in Sintrom patients and 31 determinations in patients with hepatitis).

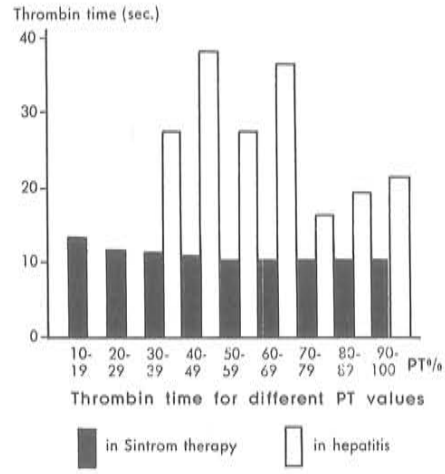

Fig. 2

Discussion

According to our observations (table 1) the decrease of activity of factor VII is about proportionate to the PT disturbance; the contention is therefore justified that during Sintrom therapy the PT depends especially on the factor VII activity. Douglas arrived at the same conclusion for another coumarin derivative: Tromexan (2). The possibility of normalizing the disturbed PT with prothrombin-free serum, as demonstrated by Douglas for Tromexan administration and by ourselves for Sintrom therapy, also pleads for the rela-

tionship between PT and factor VII during administration of coumarin derivatives.

D o u g l a s , however, goes further and concludes that the decrease of the prothrombin activity is hardly of importance for the effect of these anticoagulants. In our opinion, there is no proof for this: although the PT can be completely corrected by a prothrombin-free agent (normal serum), the thrombin generation remains disturbed and its correction becomes better the more prothrombin is present in the correcting agent (table 2). Investigations of L a s c h and R o k a have shown that prothrombin is formed from factor VII in the presence of vitamin K and liver mitochondria (3). Based on such observations, we may perhaps *a priori* expect a certain relationship between the activities of the two coagulation factors, and it will be considered less probable that a coumarin derivative exerts influence on only one of the two.

Conclusions

1. The decrease of activity of prothrombin, occuring during administration of "Sintrom", becomes only manifest when the activity of "factor VII" has fallen to less than half its normal value.

2. The behaviour of the thrombin time is the manifestation of an important difference between the coagulation defect in hepatitis and that on administration of Sintrom.

Résumé

1. La diminution du taux de prothrombine, après administration de "Sintrom", ne devient manifeste que quand le taux du "facteur VII" est descendu à 50% de la valeur initiale.

2. Le temps de thrombine est différent dans les cas d'hépatite et après administration de Sintrom ce qui suggère une différence importante entre ces deux états.

Zusammenfassung

1. Die Verminderung der Aktivität von Prothrombin wird bei Verabreichung von Sintrom nur dann manifest, wenn die Aktivität des „Faktor VII" auf weniger als die Hälfte des Normalwertes abgesunken ist.

2. Das Verhalten der Thrombinzeit zeigt eine deutliche Differenz zwischen der Gerinnungsstörung bei Hepatitis und derjenigen nach Anwendung von Sintrom.

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