An Evaluation of a New Anticoagulant, Acenocoumarin (Sintrom)

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A new coumarin anticoagulant, acenocoumarin (Sintrom) is compared with other hypoprothrombinemic agents in the same human subjects. Comparing doses which result in the same peak prothrombin time, both speed of onset and duration of effect are found to be a function of the rate of biotransformation. Rapid biotransformation results in fast onset and short duration of action and vice versa. Sintrom is intermediate between the slow, long-acting compounds (Dicumarol, Warfarin, Coumopyrin) and the fast, short-acting Tromexan. One 16 to 32 mg. dose of Sintrom rapidly results in a desirable hypoprothrombinemia which is maintained by a single daily dose of 2 to 10 mg.

Since the introduction of Dicumarol about 15 years ago, more than a half dozen additional hypoprothrombinemic agents have become available. Because of wide species differences, comparative pharmacologic studies in animals have been of little value in determining the relative merits of these compounds in man. Empirical clinical comparisons of all these compounds in large numbers of patients by any one group of investigators is an almost impossible task. On the other hand, studies of the comparative human pharmacology of these compounds in the same group of individuals represents a rational method for evaluating their properties and hence their probable advantages and disadvantages. This paper describes the application of this concept to a new coumarin compound, acinocoumarin (Sintrom) (G 23350).*

All known coumarin and indanedione anticoagulants apparently have the same fundamental mechanism of action, i.e., an inhibition or alteration in the synthesis of a portion of the prothrombin complex. The differences in activity of these compounds are related primarily to (1) rate and completeness of absorption; (2) rate of metabolism and/or excretion and (3) potency (i.e., amount of drug necessary to achieve a given response). These factors can best be studied by determining the fate of each compound by chemical methods, and correlating this with the prothrombin response. Such studies have previously been carried out in man with four compounds: bis hydroxy-coumarin (Dicumarol),* ethyl biscoumacetate (Tromexan),* phenindione (Danilone) (Hedulin),* and 3-(alpha-acetonylbenzyl) 4-hydroxy coumarin (Warfarin).* These studies have resulted in the following:

1. No compound induces a detectable prothrombin change in less than 6 to 12 hours even when given intravenously in large doses. So-called therapeutic prothrombin levels are rarely achieved in less than 18 to 24 hours.

2. The duration of prothrombin response is directly related to the persistence of the drug in plasma, i.e., following a single intravenous dose, the more rapidly the drug disappears from plasma, the shorter will be the duration of the prothrombin response (table 1). There is considerable variation in the rate of disappearance of the same drug in different subjects* and these differences are reflected in the duration of prothrombin response.

3. There are wide individual variations in the sensitivity of prothrombin response to a given drug plasma level, i.e., the same drug level in different subjects may result in quite different prothrombin time peaks.*

4. Hypoprothrombinemic agents with relatively short duration of action tend to produce a more rapid initial prothrombin response. Conversely, drugs with prolonged duration of

* Sintrom was kindly supplied to us by Dr. Albert Hemming of Geigy Pharmaceuticals, Division of Geigy Chemical Corp., New York, N. Y.

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TABLE 1.—Duration of Prothrombin Response After Single Doses of Various Agents in Man

(Doses compared are those which give the same maximum prothrombin time, viz. 23 sec. in whole plasma (control, 13.5 sec.))

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg.)</th>
<th>Day of Prothrombin Peak</th>
<th>Day of Prothrombin Recovery</th>
<th>Half-life in Man (hrs.)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tromexan</td>
<td>1650</td>
<td>1</td>
<td>2</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>Sintrom</td>
<td>20</td>
<td>1-2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylindanedione</td>
<td>350</td>
<td>2</td>
<td>4</td>
<td>6.5</td>
<td>3</td>
</tr>
<tr>
<td>Dicumarol</td>
<td>400</td>
<td>2-3</td>
<td>5</td>
<td>32.0</td>
<td>1</td>
</tr>
<tr>
<td>Cumopyran (63)</td>
<td>150</td>
<td>2-3</td>
<td>5-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin (42)</td>
<td>65</td>
<td>2-3</td>
<td>5-6</td>
<td>90.0</td>
<td>4</td>
</tr>
<tr>
<td>Mareumar</td>
<td>24</td>
<td>2-3</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipaxin</td>
<td>20</td>
<td>3-4</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

action have a slower onset of hypoprothrombinemia. The speed with which a given prothrombin response is achieved also varies greatly with the dose given. Slow, long-acting hypoprothrombinemic agents can be given in large enough doses to induce a relatively rapid onset of response. However, such large doses may subsequently cause excessive prothrombin deficiency. Comparisons of different drugs regarding speed of onset of effect therefore require that a method be devised for determining which dose of Drug A should properly be compared with a given dose of Drug B. As a rule, the more rapidly the drug is eliminated, the more safely can a rapid onset of effect be induced.

The determination of coumarin or indanedione drug levels by methods previously reported requires that the drug be present in plasma in amounts greater than 5 mg. per liter if the rate of disappearance is to be determined. The potency of Sintrom precludes its administration in man in sufficiently large doses to permit significant measurements by these technics. Consequently, prothrombin response is the only basis available in man at present for comparing this drug with other hypoprothrombinemic agents.

Sintrom (acenocoumarin, G-23350), synthesized by Stoll and Litvan, is a coumarin compound with the following structural formula:

\[
\text{CH}_3
\]

\[
\text{CO}
\]

\[
\text{OH}
\]

\[
\text{CH}_2
\]

\[
\text{NO}_2
\]

Pharmacologic studies by Pulver have demonstrated its anticoagulant properties and several clinical reports have appeared in Europe.

**ExPERIMENTAL STUDIES**

Single Doses

In order to compare the speed of onset and duration of effect of various hypoprothrombinemic agents in man, it is necessary to determine what single dose of each compound, tested in the same subject, would give the same peak prothrombin response. In our studies, a prothrombin time of 23 seconds (equivalent to 50 seconds in 12.5 per cent saline-diluted plasma) was chosen as the peak prothrombin effect to be sought in each subject with single doses of each drug. The prothrombin response to various single doses of eight different hypoprothrombinemic agents was studied in each of five subjects. In each instance, at least one week was allowed to elapse between recovery from the previous dose and administration of the next dose. The dose necessary to achieve a peak prothrombin response of 23 seconds (control 13.5 seconds) was thus determined for each drug in each subject. The average dose necessary for this response and the average pattern of the response are summarized in table 1 and figure 1. The half-life of each drug in plasma, as determined by chemical methods applicable to studies in man, is also given in table 1. In this table, the drugs were arranged

* The thromboplastin used was Simplastin, kindly supplied by Dr. George Phillips of the Chilcott Laboratories. The normal prothrombin time with this preparation was 13.5 seconds.
according to speed of prothrombin response. This same arrangement also holds for speed of recovery of normal prothrombin activity. Neither speed of response nor of recovery correlated with "potency" (with milligrams of drug required to achieve a given peak prothrombin response). The rate of drug metabolism in man as previously determined by chemical methods for four of these drugs does correlate with speed of prothrombin response and recovery.

The data indicate that Sintron, like phenylindanedione, is slower acting than Tromexan, but distinctly faster acting than Dicumarol. Its potency is considerably greater than that of Tromexan, phenylindanedione or Dicumarol.

**Multiple Doses**

Fifteen patients were treated with Sintron for a total of 444 patient-days, controlled by 280 prothrombin time determinations. Of these prothrombin determinations (exclusive of the first day of treatment) 39 were below 20 seconds, and 7 were above 40 seconds. Maintenance dosage varied from 2 to 10 mg. per day following an initial dose of 16 to 32 mg. The prothrombin time was above 20 seconds in 10 of the 15 patients 24 hours after the initial dose. Prothrombin time returned to normal within one to two days of the last dose in 14 of the 15 patients treated.

Gross hematuria developed in one subject at a prothrombin time of 48 seconds. Hematuria disappeared within 24 hours of discontinuing dosage. No vitamin K was given. There were no other instances of hemorrhage. In one patient who was very sensitive to the drug, rapid fluctuations in prothrombin response were noted, making control difficult. All others were readily maintained in the desired range of prothrombin activity by daily doses of from 2 to 10 mg. There was no instance of "resistance" to Sintron.

Three patients have been maintained for alternating periods on Sintron and phenylindanedione. The ratio of the daily doses of each drug which maintained the same prothrombin time was the same in all 3 patients, i.e., 4 mg. of Sintron were approximately equivalent to 100 mg. of phenylindanedione.

**Discussion**

If one considers the previously established relationships of drug plasma level to prothrombin response to other drugs, one might infer the probable metabolic rate of Sintron by comparing its prothrombin pattern with that of other drugs (fig. 1). These data indicate that Sintron acts at a rate very similar to that of phenylindanedione, i.e., distinctly more rapid than Dicumarol, but somewhat slower than Tromexan. One might, therefore, predict that with proper initial dosage, "therapeutic" prothrombin levels usually will be achieved within 24 hours, with little danger of a subsequent excessive rise. Repeated daily doses will then be necessary to maintain effect. Discontinuing therapy will result in a prompt return of prothrombin time to near normal in one to two days. These deductions are borne out by the brief clinical experience here presented.

**Summary**

1. Sintron, a new coumarin anticoagulant, has been compared with other oral anticoagulants in single doses in the same individuals. It is more rapidly acting than Dicumarol and somewhat slower than Tromexan. In this respect, it closely resembles phenylindanedione.

2. Clinical experience with 444 patient-days of treatment in 15 subjects indicates that a desired degree of hypoprothrombinemia can be rapidly obtained and effectively maintained with this compound. In only one individual were prothrombin time fluctuations so rapid as to make control difficult.

3. No toxic manifestations were noted ex-
cept for one instance of hematuria which was controlled by discontinuing therapy.

4. The properties of Sintrum permit a relatively rapid onset and recovery of hypoprothrombinemia with less likelihood of the very rapid fluctuations of prothrombin time which sometimes results from more rapidly metabolized drugs. In this sense, it strikes a balance between slow, long-acting compounds (Dicumarol, Marcoumar, Warfarin, Coumopyrin) and the very fast, short-acting compound, Tromexan.

5. In terms of milligrams, Sintrum is 25 times as potent as phenylindanedione.

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An Evaluation of a New Anticoagulant, Acenocoumarin (Sintrom)
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