Marcumar [3-(1'-phenyl-propyl)-4-hydroxycoumarin]. A New Anticoagulant

By René Bourgain, M.D., Margaret Todd, B.S., Lorraine Herzig, B.A., and Irving S. Wright, M.D.

Marcumar [3-(1'-phenyl-propyl)-4-hydroxycoumarin] is a new anticoagulant. Marcumar acts more rapidly than Dicumarol, but not quite as rapidly as Tromexan. The action is more prolonged than Dicumarol. As with other anticoagulants, the administration of Marcumar requires conscientious observation and accurate prothrombin complex determinations.

In the last two decades the use of anti-coagulant therapy for thromboembolic disorders has become generally accepted. The hypoprothrombinemic action of certain coumarin derivatives made these drugs valuable anticoagulants. However, Dicumarol (3-3'-methylenebis-4-hydroxycoumarin) and Tromexan (3, 3'-carboxymethylenebis-4-hydroxycoumarin ethyl ester), although frequently prescribed, have their disadvantages. The prolonged delay before anticoagulant activity can be detected with the former and the rapidly disappearing effect on the blood clotting mechanism of the latter stimulated research with other coumarin derivatives. In recent years efforts were directed to the synthesis of an anticoagulant with a short latent period following administration and a moderate cumulative effect, thus facilitating control. In the last year anticoagulant properties of a compound called Marcumar [3-(1'-phenyl-propyl)-4-hydroxycoumarin] were described by Koller and Jakob and Jürgens. On equal weight basis these investigators observed a higher anticoagulant activity for Marcumar than Dicumarol, and described an antagonistic effect of vitamin K, for this new drug. Matis, Hartert and Hartert, Thies, and De Nicola and co-workers confirmed these observations independently. The action of Marcumar on the dilute and undilute prothrombin complex time, proconvertin time, and prothrombin time after oral and intravenous administration to rabbits and after oral administration to humans are described herein.

Methods and Materials

Prothrombin complex time* determinations were done by the Link-Shapiro modification of Quick's one-stage method on undiluted and diluted plasma (12.5 per cent in normal saline). A prolonged dilute prothrombin complex time (D.P.C.T.) or undilute prothrombin complex time (U.P.C.T.) may be due to a decrease in proconvertin or prothrombin or both.

Proconvertin times were performed by the method described by Owren.

The determination of the prothrombin level was done by adding 0.1 ml. of a mixture of equal amounts of stored serum and plasma treated with barium carbonate to 0.1 ml. of the diluted plasma to be examined (10 per cent in normal saline). The clotting time obtained after addition of calcium-thromboplastin to this mixture reflects exclusively the activity of the prothrombin.

The thromboplastin used in the above-mentioned determinations was prepared in our laboratory from dried rabbit lung. The calcium chloride used was a 0.025 molar solution.

As rabbits manifest important differences in sensitivity to coumarin derivatives after oral administration, only animals which develop a dilute prothrombin time of 60 seconds or more for at least one day after oral administration of 2.5 mg. Dicumarol were accepted for study with Marcumar.

Results

Control studies on normal rabbit plasma were done in 60 animals. The average values ob-

* Since the methods of Quick and Link-Shapiro measure a complex substance of which proconvertin and prothrombin are important factors, the term complex will be used to differentiate this mixture from determinations of prothrombin alone.

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Aided by grants from the Kress, Lasker, Hyde and Hampil Foundations.
TABLE 1.—Control Values for the Undilute (U.P.C.T.) and Dilute Prothrombin Complex Times (D.P.C.T.), Proconvertin Time and Prothrombin Time of Rabbit Plasma (80 Animals)

<table>
<thead>
<tr>
<th></th>
<th>Avg (sec.)</th>
<th>Range (sec.)</th>
<th>S. D. (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.P.C.T..............</td>
<td>8.5</td>
<td>7.2-9.7</td>
<td>±0.7</td>
</tr>
<tr>
<td>D.P.C.T..............</td>
<td>22.3</td>
<td>20.0-28.0</td>
<td>±2.7</td>
</tr>
<tr>
<td>Proconvertin time...</td>
<td>22.9</td>
<td>18.5-27.4</td>
<td>±2.2</td>
</tr>
<tr>
<td>Prothrombin time....</td>
<td>14.0</td>
<td>10.2-16.1</td>
<td>±1.9</td>
</tr>
</tbody>
</table>

served for the undilute and the dilute prothrombin complex times, the proconvertin time and the prothrombin time are shown in table 1.

A single dose of 2.5 mg. Marcumar per kilogram of body weight was administered orally to 11 animals after 48 hours starvation. Food was withheld for five more days. Evidence of anticoagulant activity was detected 12 hours after administration. At that time the proconvertin time was prolonged (average, 47 seconds), but this hypoconvertinemia was not sufficient to prolong the dilute or undilute prothrombin complex times significantly. The dilute and undilute prothrombin complex times became prolonged after 18 hours, and reached a maximum value on the second day after the administration of the drug. The curve observed for the proconvertin time is similar to the curve observed for the undilute and dilute prothrombin complex times. The prothrombin, however, was decreased between 18 and 24 hours and maximal decreases were observed between the second and third day. The activity evidenced by a prolongation of the undilute and dilute prothrombin complex times lasted from four to five days.

Under the same experimental conditions 4 mg. of Marcumar per kilogram were given orally to 10 animals, and 10 mg. of Marcumar per kilogram were given to four animals. Similar findings were observed as after the oral dose of 2.5 mg. of Marcumar per kilogram. In both groups the peak of anticoagulant activity occurred after two days and the effect disappeared on the fifth day as evidenced by the dilute prothrombin complex time.

To two rabbits 10 mg. of Marcumar were given intravenously. The dilute prothrombin complex times reached a peak two days later (69.2 seconds in one and 35.4 seconds in the other animal). The dilute complex time was normal after five days in the first and after four days in the other animal. The proconvertin times followed a curve similar to the dilute prothrombin complex times. The prothrombin, however, reached a minimum level between two and three days after injection.

A daily oral dose of 4 mg. of Marcumar per kilogram was given to three rabbits on normal diet. In one animal the dilute prothrombin complex time was 139.5 seconds 11 days after the initial dose, and remained at 90 seconds for six days, at which time the drug was discontinued. In a second rabbit the dilute complex time was greater than five minutes after eight days. Marcumar was then withheld. In a third animal the dilute complex time was 94.2 seconds after eight days, and remained at this level for three days. The dilute complex time became normal within 48 hours after Marcumar was discontinued in the three animals.

**Fig. 1.** Curves of average values for the dilute prothrombin complex time (B), the proconvertin time (A) and the prothrombin time (C) in 11 rabbits after oral administration of 2.5 mg. Marcumar per kilogram.

**Fig. 2.** Curves of average values for the dilute prothrombin complex time (B), the proconvertin time (A) and the prothrombin time (C) in 10 rabbits after oral administration of 4 mg. Marcumar per kilogram.
One rabbit was given a daily dose of 5 mg. of Marcumar per kilogram. This animal expired 11 days later at which time the dilute prothrombin complex time was greater than five minutes, and had been greater than 150 seconds for the last six days. On autopsy, extensive hemorrhages were found in the chest cavity and the large bowel. However, no visible renal hemorrhages were observed.

A single oral dose of 4 mg. of Marcumar per kilogram was given to two rabbits on normal diet, and a prolonged dilute prothrombin complex time was observed for two days.

**Clinical Studies**

The control values observed on normal human plasma of 40 healthy individuals for the undilute and dilute prothrombin complex times, proconvertin time and prothrombin time are shown in table 2.

A single oral dose of 18 mg. Marcumar was given to nine patients. Evidence of anticoagulant activity was detected 24 hours after administration (fig. 3). The maximum value for the undilute and dilute prothrombin com-

**Table 2.** Control Values for the Undilute and Dilute Prothrombin Complex Times, Proconvertin Time, and Prothrombin Time of Normal Human Plasma

<table>
<thead>
<tr>
<th></th>
<th>Avg. (sec.)</th>
<th>Range (sec.)</th>
<th>S. D. (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.P.C.T.</td>
<td>14.8</td>
<td>13.0–15.6</td>
<td>±1.02</td>
</tr>
<tr>
<td>D.P.C.T.</td>
<td>38.1</td>
<td>36.2–41.0</td>
<td>±2.64</td>
</tr>
<tr>
<td>Proconvertin time</td>
<td>28.7</td>
<td>25.6–30.1</td>
<td>±1.98</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>20.9</td>
<td>19.5–22.3</td>
<td>±0.05</td>
</tr>
</tbody>
</table>

**Fig. 4.** Curves of average values for the dilute prothrombin complex time (A), the proconvertin time (B) and the prothrombin time (C) in seven patients after oral administration of 21 mg. Marcumar.

Complex times occurred on the third day. At that time the average dilute time was 60 seconds. A normal dilute prothrombin time was observed on the fifth day. The peak of the proconvertin time occurred 12 to 24 hours earlier than the peak of the dilute time. Maximal decrease in prothrombin was noticed after four days (24 hours after the peak of the dilute complex time).

A single oral dose of 21 mg. Marcumar was given to seven patients. The undilute and dilute prothrombin complex times, proconvertin time, and prothrombin time were in the range of the values observed after administration of 18 mg. Marcumar. The activity lasted slightly longer; the dilute time became normal on the sixth day after administration.

Anticoagulant treatment with Marcumar was given to several patients suffering from thromboembolic diseases. After an initial dosage of 21 mg. the first day and 9 mg. the

**Fig. 5.** Evolution of the undilute prothrombin complex time in a patient suffering from thrombophlebitis and treated with Marcumar. The first day 21 mg. was given, the second and third day 9 mg., after which the drug was discontinued for three days. The administration of 9 mg. the sixth day and 3 mg. daily subsequently allowed us to keep the undilute prothrombin time within the therapeutic range.
second day, the treatment was continued by giving 3 mg. of Marcumar daily. Under these conditions, the undilute prothrombin complex time varied between 22 and 35 seconds, and the dilute time between 80 and 120 seconds. One patient received 9 mg. of Marcumar on the third day by mistake, after which the treatment was continued as indicated in figure 5. Another patient had an undilute complex time of 71 seconds and a dilute time of more than three minutes eight days after treatment was started. The administration of 100 mg. of vitamin K₁ (orally) reduced the undilute time to 52 seconds within four hours. The next day the undilute and the dilute prothrombin complex times were normal.

**DISCUSSION**

The experimental and clinical studies demonstrate and anticoagulant properties of Marcumar. Pharmacologically this drug acts by depressing both the proconvertin and the prothrombin in the plasma.

After oral or intravenous administration of Marcumar to rabbits, proconvertin is the first factor affected. The decrease of this factor can be detected usually within 12 hours after administration. The undilute and dilute prothrombin complex times, however, do not show any change before 18 hours. The peaks of the proconvertin time, and undilute and dilute complex times occur simultaneously after 48 hours. Maximal decrease in prothrombin is observed between 48 and 72 hours. Between the peak of the proconvertin time and the prothrombin time there is a 12- to 24-hour delay. The anticoagulant effect lasts between four and five days when the dosage is equal to or greater than 2.5 mg. per kilogram. Identical rates of activity are observed when Marcumar is given in dosages from 2.5 mg. per kilogram to 10 mg. per kilogram. Similar findings were observed by Overman for Dicumarol after oral administration of dosages greater than 6 mg. However, Dicumarol in doses from 2.5 mg. to 6 mg. gave a proportional rise in the dilute prothrombin complex time. This proportional increase of the dilute time was not observed with Marcumar when increasing amounts of this drug are given.

It is well known that rabbits on normal diet actively synthesize vitamin K in the intestine. The duration of anticoagulant activity after oral administration of 2.5 mg. of Marcumar per kilogram is five days when the animal is starved, but is reduced to three days when the rabbit is on normal diet. Under the same conditions the anticoagulant activity of Marcumar after intravenous injection of 10 mg. is reduced from four days to one day. These findings suggest the antagonistic effect of vitamin K on the anticoagulant activity of Marcumar.

The oral administration of 18 mg. of Marcumar to humans results in prolonged dilute and undilute prothrombin complex times, a maximum being reached on the third day after administration. On the fifth day normal values are observed. Similar results are found after administration of 21 mg. of Marcumar except for a more prolonged duration of action. The prothrombin complex time determined by the dilute method returns to normal on the sixth day. The proconvertin time is prolonged within 18 hours, reaching a peak after two days. The prothrombin presents a maximal decrease between the third and fourth day. The peaks of the undilute and the dilute complex times occur on the third day. The anticoagulant activity evidenced by prolonged undilute and dilute prothrombin complex times lasts four to five days. These findings demonstrate and confirm the prolonged duration of activity related to Marcumar.

The administration of 3 mg. Marcumar daily after the initial dose of 21 mg. on the first day and 9 mg. on the second day usually keeps the dilute and undilute prothrombin complex times within the limits of therapeutic value. (The time by the undilute method is between 20 and 35 seconds, by the dilute method between 70 and 160 seconds.) Compared with Dicumarol, Marcumar is much more active in humans. In patients, the daily dosage required after stabilization of the dilute and undilute complex times in the therapeutic range is equal to or smaller than 3 mg. This means an average activity 20 times that of Dicumarol. Marcumar is a more rapidly acting drug than Dicumarol, but it is frequently not as rapid as Tromexan. Evidence of antico-
agulant activity can usually be detected between 18 and 24 hours after administration.

**Summary**

Marcumar [3-([1′-phenyl-propyl]-4-hydroxy-coumarin) is a new anticoagulant. It has been studied in animals and in humans subjects. It is suitable and effective for anticoagulant therapy. Anticoagulant activity can be detected for four to five days in rabbits after one single oral dose of 2.5 mg. per kilogram, and for five days in humans after one single dose of 18 mg. The administration of higher doses to rabbits gives a response similar to that produced by 2.5 mg. per kilogram. However, in humans the increase in dosage seems to prolong slightly the duration of activity. In patients the therapeutic optimum can be obtained when 21 mg. Marcumar is given the first day and 9 mg. the second day. The administration of 3 mg. daily usually keeps the undilute prothrombin complex time and dilute prothrombin complex time within the therapeutic range. The dosage requirements vary between patients, and in the same patient from day to day. There is also a tendency for the effect to accumulate over a period of time on the same dosage. As with all other coumarins, conscientious observation and frequent checking of the undilute prothrombin complex time and dilute prothrombin complex time are essential to safe therapy.

**Sumario Español**

Marcumar [3-([1′-fenil-propil]-4-hidroxi-cumarin) es un nuevo anticoagulante. Se ha estudiado en animales y sujetos humanos. Es apropiado y efectivo en la terapia anticoagulante. Actividad anticoagulante se puede percibir por cuatro o cinco días en conejos luego de una sencilla dosis de 2.5 mg. por kilogramo y por cinco días en el humano luego de una dosis de 18 mg. La administración de dosis mayores a conejos produce una repuesta similar a la producida por 2.5 mg. por kilogramo. Sin embargo, en humanos el aumento en dosis parece prolongar ligeramente la duración de actividad. En pacientes, el óptimo terapéutico se puede obtener cuando 21 mg. de Marcumar se administran el primer día y 9 mg. el segundo día. La administración de 3 mg. diarios usualmente mantiene el tiempo del complejo de protrombina no diluido y el tiempo del complejo de protrombina diluido entre el margen terapéutico. Los requerimientos en dosis varían entre pacientes y en el mismo paciente de día en día. También hay una tendencia en el efecto de ser cumulativo luego de un período de tiempo con la misma dosis. Como con todos los otros coumarins, observación concienzuda y una verificación frecuente del tiempo del complejo de protrombina no diluido y del tiempo del complejo de protrombina diluido son esenciales para la terapia sin peligro.

**Acknowledgments**

Acknowledgment is made to Dr. Leo A. Pirk of Hoffmann-LaRoche, Inc., Nutley, N. J., for supplies of Marcumar.

We are grateful to Dr. Ellen McDevitt, Chief of the Vascular Clinic, Bellevue Hospital, 2nd (Cornell) Medical Division, for her valuable help in providing patients for this study.

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doi: 10.1161/01.CIR.10.5.680
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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