

## Oral Anticoagulant Therapy and its Control: Marcumar(Phenprocoumon), a new highly active Anticoagulant and Konakion (Phytomenadione), as an Effective Regulator

Charles E. Brambel and G. Lawrence Serra  
University of Notre Dame and University of Maryland  
Notre Dame, Indiana and Baltimore, Maryland

Therapy involving the use of drugs which impair the coagulability of blood is now generally known as "anticoagulant therapy". The objectives of such a procedure involve the impairment of the clotting system of the blood to such a degree that intravascular thrombosis is prevented. However, the induced hypocoagulability of the blood must not be accompanied by serious hemorrhagic complications. Recent developments have provided new principles which show promise of improvement in safety and efficacy of such therapy in thrombosis and embolism.

The clinical use of oral anticoagulants is now widely recognized as the best procedure for the treatment and prevention of intravascular clotting. Successful anticoagulant therapy may be employed for short-term and long-term periods. The work of F. Janney Smith and Irving S. Wright attests to the usefulness of long-term anticoagulant therapy in intracardiac thrombosis. During the course of our studies patients have received anticoagulant drugs from three months to nine years. The practicality of such a routine procedure has been established. The advisability and clinical efficacy will become apparent with time.

The regulation of oral anticoagulant therapy involves the choice of an anticlotting drug and the maintenance of therapeutic impairment of the blood clotting system. Wide deviations of blood coagulability in either direction may result in highly undesirable consequences, namely, intravascular clotting or hemorrhage. Since all oral inhibitors of blood coagulation exhibit a time lag before onset of the desired effect, the importance of increasing predictability of response becomes apparent.

In our experience, highly active oral anticoagulants give greater predictability of response than less active compounds. Also, the former have a more

sustained or prolonged anticoagulant effect. Such an effect is more desirable than erratic periods of borderline therapeutic ranges frequently seen with less active drugs. Figures 1 and 2, taken from the published record, show the undesirable effects from a weak oral anticoagulant: erratic response may result in hemorrhagic complications or in recurrence of thrombotic episodes. By the same token there may be little response from large doses and exaggerated response from small doses. Controllability of anticoagulant effect is reduced to a minimum even with daily testing of the patient. Such data indicate that drugs of low potency are not suitable for long-term anticoagulant therapy because of unpredictability of effect. These data have been confirmed by us.

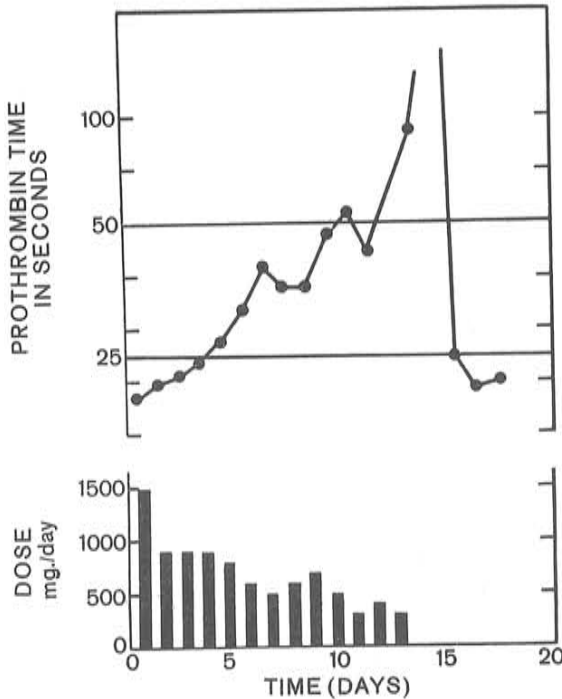


Fig. 1: Figures 1 and 2 are reproduced by courtesy of M. Weiner, M.D. and the Amer. J. Med. (Weiner, M. et al., Amer. J. Med. 14: 689 [1953]).

This study involves 1,146 patients who were given Marcumar alone, or Marcumar after they had received some other anticoagulant, or Marcumar and vitamin K<sub>1</sub>. As is seen from table 1, 970 patients of the former series were designated as "ultra-short" cases (patients who received 1—3 doses of Marcumar); 121 as "short-term" cases (patients who received 4 or more doses of Marcumar, but were treated for no longer than 27 days); and 55 as "long-

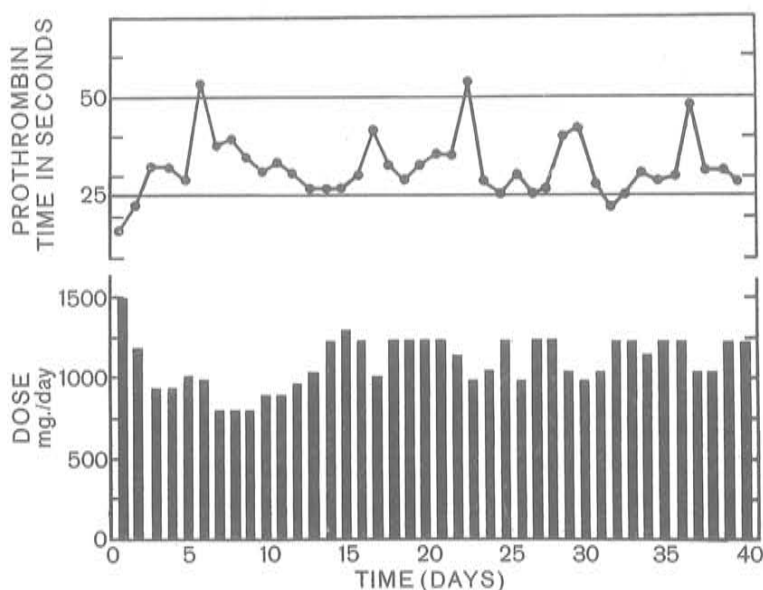


Fig. 2

term" cases (patients who received Marcumar for 28 or more days, with an average of 367.5 days). The table shows also classification of these patients according to type of medical care, total number of Marcumar doses and total number of treatment days.

Tab. 1: 1,146 patients treated with Marcumar; Their classification according to duration of treatment; Sex distribution; Average age; Type of medical care; Total number of Marcumar doses; Total number of days under treatment.

Classification according to duration of treatment	No. of cases	Sex		Average age (years)	Type medical care				Total no. Marcumar doses	Total no. treatment days
		male	female		ob.	surg.	gyn.	med.		
Group 1: Ultra short	970	36	934	28.8	887	57	14	12	1,422	4,775
Group 2: Short term	121	48	73	46.2	22	68	13	18	1,015	2,330
Group 3: Long term	55	40	15	53.3	—	6	—	49	11,572	20,135
Total	1,146	124	1,022	31.5	909	131	27	79	14,009	27,240

Five hundred and seventy-six patients of the "ultra-short" cases were given single Marcumar doses which ranged from 9—40 mg. The effects of single doses

of 20, 30 and 40 mg Marcumar were further investigated. Figure 3 shows the results with these doses in 110, 306 and 107 patients, respectively. As is seen, for the 306 patients who received single 30 mg doses of Marcumar, the average prothrombin clotting time values in whole plasma with the one stage procedure, ranged from 23.3—28.5 seconds, i.e., the averages of findings from 38 hours after drug administration were ideally within the selected therapeutic range of 20—30 seconds (indicated by center band on the figure). With single 20 mg doses the average prothrombin clotting time assays were somewhat lower though still within the desired range, but with single 40 mg doses they were partly above 30 seconds. In general, there was good dose-response relationship.

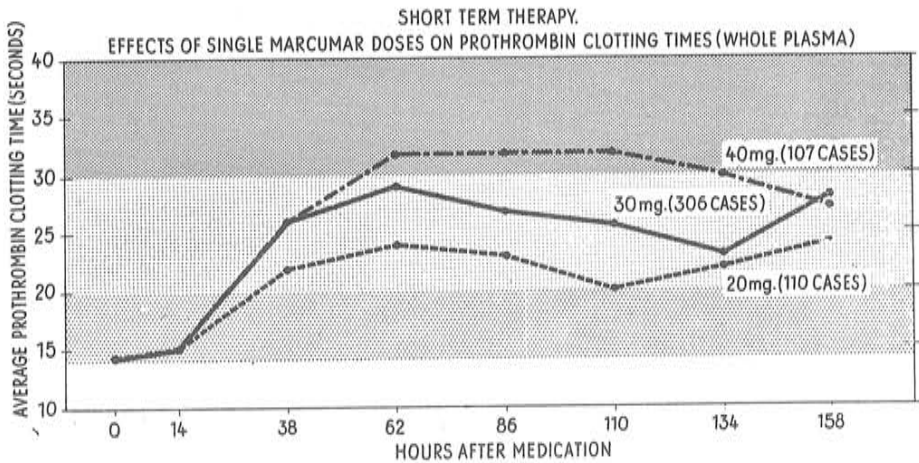


Fig. 3

The center portion of the next figure shows the percentage of assays which fell within the desired range, above 30 seconds and under 20 seconds, respectively, at 38, 62 and 86 hours after the 30 mg single dose administration (Fig. 4). It appears that 84, 59 and 67% of the prothrombin clotting time values at these times were within the therapeutic range\*) (top line). The corresponding figures for the values above 30 seconds and below 20 seconds were 10, 36 and 27% for the former (center line) and 6, 5 and 6% for the latter (bottom line). A further analysis of the "over-shoots" and "under-shoots" revealed that at 38 hours 65% and 80%; at 62 hours 32% and 66% and at 86 hours 60% and 50% of the assays were marginal to 30 seconds and 20 seconds, respectively. Since the differences between these marginal values and the upper and lower

\*) It is to be noted that the therapeutic range changes if another thromboplastin preparation with a different activity is used.

limits of the therapeutic range were within the experimental error it can be safely stated that 95.8%, 73.8% and 86.2% of the assays carried out at 38, 62 and 86 hours, respectively, may be considered within the therapeutic range.

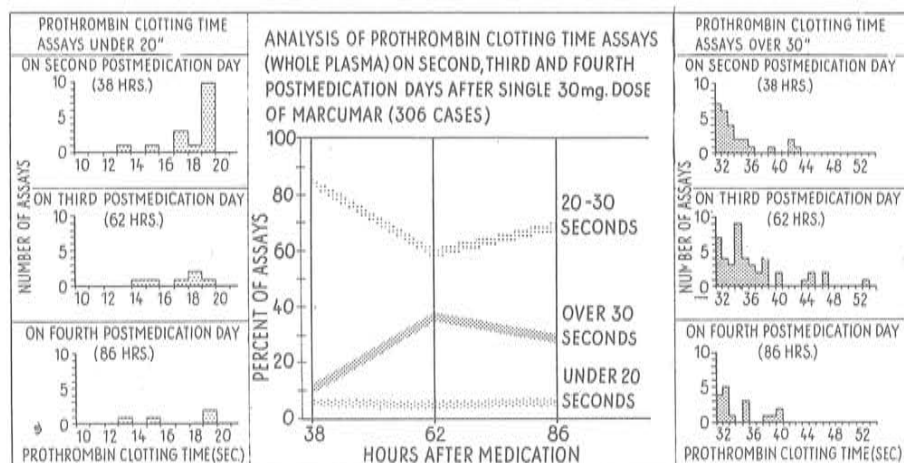


Fig. 4

These data reflect the dependability of response and ease of maintenance of a selected degree of impairment of the blood clotting mechanism up to 86 hours after a single Marcumar dose. Such conditions are highly desirable and most essential for effective anticoagulant therapy during short-term treatment. In contrast, single doses of less potent drugs gave 25—40% therapeutic responses both in our hands and in those of other workers.

Small daily Marcumar doses (average 2 mg) are required for the maintenance of a selected therapeutic level of impairment of the blood clotting system for months or even years. Three hundred patients have been studied who received Marcumar for periods varying from one month to over one year. Satisfactory therapeutic levels were maintained in these patients. Of these 300 patients, the data pertaining to 55 unselected cases were analysed (Table 2).

They received 20,135 Marcumar doses over a period of 11,572 treatment days. Of the 2,923 prothrombin clotting time assays performed, 68.9% fell within the desired range of 20—30 seconds. Only 4.2% were above 30 seconds and 24.9% below 20 seconds. In a similar group of 100 patients (Table 3), who received less active anticoagulants for 38,300 treatment days, 52.3% of the 6,745 prothrombin time assays performed were between 20 and 30 seconds, 8.1% above 30 seconds and 34.8% below 20 seconds. These figures show the greater dependability of response and greater ease of maintenance of a selected

degree of impairment of the blood clotting mechanism during long-term anticoagulant therapy with Marcumar, as compared with less active drugs.

Tab. 2: Analysis of 55 patients treated with Marcumar.

20,135 treatment days
2,923 prothrombin clotting time assays
2,013 (68.9%): 20—30 seconds
728 (24.9%): 14—19 seconds
124 (4.2%): 31—35 seconds
58 (2%): 36 seconds and over
Oral Konakion doses given — — 9
Hemorrhagic complications — — 0 cases
300 patients were treated with Marcumar for prolonged periods with results as shown in above sample.

Tab. 3: Analysis of 100 patients treated with less active anticoagulants

38,300 treatment days
6,745 prothrombin clotting time assays
3,518 (52.3%): 20—30 seconds
2,340 (34.8%): 14—19 seconds
544 (8.1%): 31—35 seconds
323 (4.8%): 36 seconds and over
Vitamin K <sub>1</sub> doses given — — 42
Hemorrhagic complications — — 4 cases.

The sustained effect of highly active anticoagulant drugs is not undesirable if the degree of inhibition of the blood clotting mechanism can be regulated. Such regulation can be accomplished by 10—30 mg oral doses of vitamin K<sub>1</sub> — Konakion — without the danger of producing refractoriness to further administration of anticoagulant drugs. With higher doses, used in previous work, refractoriness to continued anticoagulant treatment frequently ensued.

When severe hemorrhage associated with overdosage or hyperreaction to an anticoagulant is encountered, drastic measures are imperative. Fifty mg of Konakion should be given intravenously in this situation. Such an occasion did not arise in the series of cases on Marcumar, but there were 4 patients with hemorrhagic complications in the series of cases on less active anticoagulants.

In the event of elective or emergency surgery during anticoagulant therapy, vitamin K<sub>1</sub> may be given orally before the operation. Hyperreaction to Konakion was not encountered postoperatively following 100 mg doses given orally before surgery.

Hyperreaction (without hemorrhagic complications) to Marcumar occurred in eight of our long-term patients. Over-correction is undesirable and may be

potentially hazardous. Ten to 50 mg doses of Konakion were given orally which restored the patients prothrombin clotting time values to the therapeutic range. Under these circumstances refractoriness to further administration of Marcumar was not encountered.

### Conclusions

1. A highly active, oral anticoagulant, Marcumar, gives greater predictability of response than less active compounds.

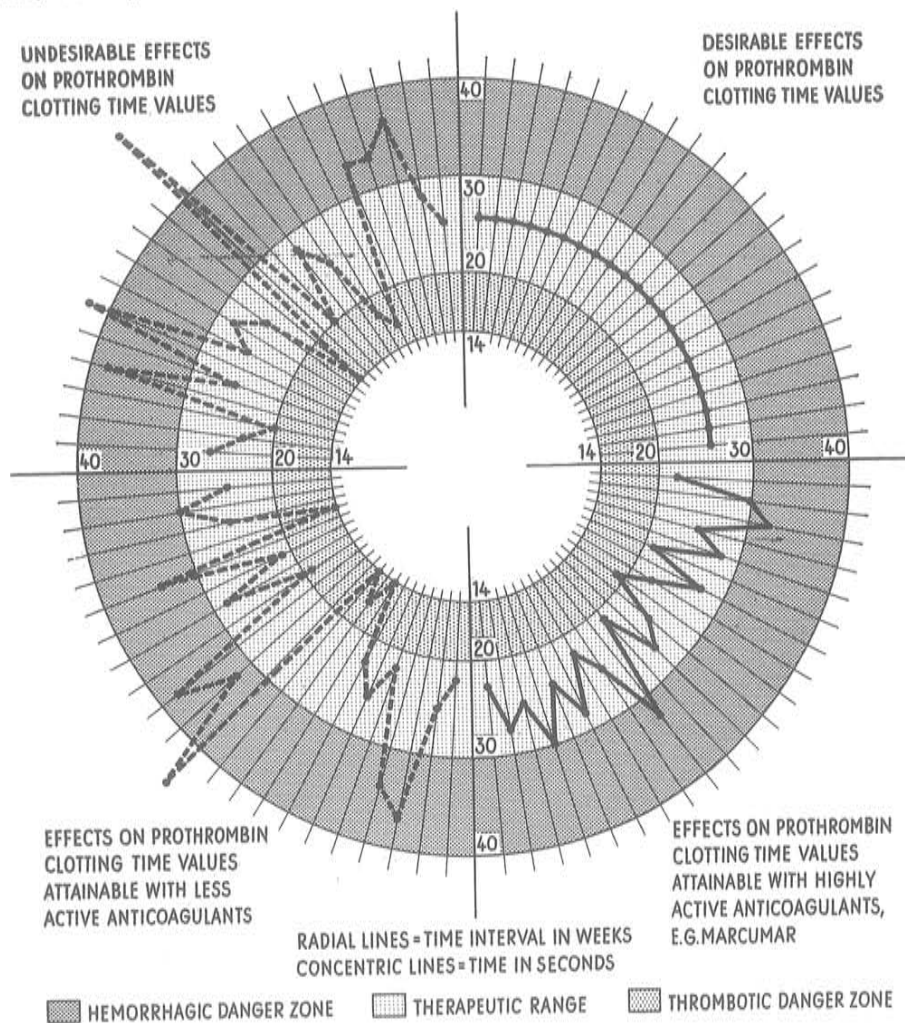


Fig. 5:

2. Maintenance of selected therapeutic prothrombin levels can be achieved with greater facility with Marcumar. Advantages of this compound are:

- a) prolonged effect insures patient protection.
- b) "under-shoots" are greatly diminished.
- c) "over-shoots" can be regulated with vitamin K<sub>1</sub>.

3. Vitamin K<sub>1</sub>, e.g. Konakion, given orally in small doses, has a regulatory effect without producing refractoriness to the further administration of the anticoagulant.

4. The use of Konakion in conjunction with Marcumar diminishes potential hemorrhagic hazards and results in greater likelihood of maintaining selected, induced levels of hypocoagulability. This is accomplished by:

- a) controlling alarming hyperreaction during short-term or long-term anticoagulant therapy.
- b) interruption of anticoagulant therapy for elective or emergency surgery.

The upper section of the last figure shows schematically the undesirable and desirable effects of coumarin-type preparations on prothrombin clotting times and the lower section indicates the attainable effects with anticoagulants of low potency and high activity (Fig. 5).

### Summary

Data are presented to demonstrate the advantages of Marcumar in short-term and long-term treatment, over less active anticoagulants, and the effectiveness of Konakion as regulator of such therapy.

### Résumé

Au cours de traitements de courte ou de longue durée, les avantages du Marcoumar sur les anticoagulants moins actifs sont mis en évidence de même que l'efficacité du Konakion en tant que régulateur.

### Zusammenfassung

Die Überlegenheit der Kurzzeit- und Langzeit-Behandlung mit Marcumar über die Anwendung geringer wirksamer Antikoagulantien wird belegt; zugleich wird die Brauchbarkeit von Konakion zur Steuerung dieser Therapie gezeigt.