PHENYLPROPYL-HYDROXYCOUMARIN AS AN ANTICOAGULANT

BY

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Many reports (Hartert and Hartert, 1953; Matis, 1953; Bourgain *et al.*, 1954; Sailer and Kresbach, 1955, etc.) on the use of phenylpropyl-hydroxycoumarin ("marcoumar") have appeared since the original accounts by Jürgens (1953) and Koller and Jakob (1953). They all show it to be very long acting, the anticoagulant effect lasting for 7 to 14 days after the last dose. It appears that the incidence of haemorrhage with phenylpropyl-hydroxycoumarin therapy is low and that the drug has a fairly stable action.

The present paper is a report on the use of phenylpropyl-hydroxycoumarin in 104 patients. Most of them were suffering from coronary thrombosis or phlebotrombosis, and in several there was evidence of cardiac failure. Quick's one-stage method was used for estimating the prothrombin time, and the thromboplastin was a phenol-saline emulsion prepared from human brain. The normal control prothrombin time with this preparation was 13 to 14 seconds, and therapeutic prothrombin levels of 20% to 10% (or approximately two to three times the normal prothrombin time) were aimed at.

Rapidity of Action and Recovery

The time necessary for the attainment of a therapeutic prothrombin time with any anticoagulant depends not only on the speed of action of the drug but also to some extent on the initial dosage. Within certain limits, the larger the commencing dose the shorter the time required to achieve the necessary rise in the prothrombin time. In this trial three different initial doses were used—namely, 21, 24, and 30 mg. The second dose (usually given 24 to 36 hours after the first dose) depended on the prothrombin time reached 24 to 36 hours after the initial dose, and varied from 3 to 15 mg. The largest total amount of phenylpropyl-hydroxycoumarin given within 48 hours was 45 mg.

With an initial dose of 21 mg., given to 10 patients, a satisfactory therapeutic prothrombin time was reached in 70% in 48 hours (in 30% in 36 hours), but not until more than 48 hours in the remaining 30%. In the second series of 35 patients who had a commencing dose of 24 mg., a therapeutic prothrombin time was attained in 84% in 48 hours (36% in 36 hours). With an initial dose of 30 mg. a therapeutic response was reached in 93% of a series of 59 cases in 48 hours (66% in 36 hours).

Phenylpropyl-hydroxycoumarin is therefore a relatively slow-acting anticoagulant requiring 48 hours to have a therapeutic effect. Initial doses in the region of 30 mg. will considerably hasten the action of the drug, but doses as large as 30 mg. require great caution in their use and should be used only for a minimum number of patients (see below).

This drug has a prolonged cumulative action. The duration of its effect depends on the level to which the prothrombin has been reduced. If the prothrombin concentration has been reduced to below 10% of normal, with a corresponding prothrombin time in the region of 50 seconds or over, it may take 7 to 14 days for the prothrombin level to rise above 50% of normal. Within the therapeutic prothrombin range of 20% to 10% (prothrombin times of 30 to 45 seconds), it usually takes four to five days for the prothrombin level to rise above 50%. As with all anticoagulants, any lowering of renal or liver function will delay the excretion and breakdown of the drug, and so further prolong its action.

Dosage

The dose of phenylpropyl-hydroxycoumarin usually recommended is 21 mg. on the first day, followed by a standard dose of 9 mg. on the second day. This dosage was tried in a small series of 10 cases, but 70% took 48 hours to reach a satisfactory prothrombin time. Therefore, in the next series of 35 cases the initial dose was increased to 24 mg., with a second dose varying up to a maximum of 15 mg. according to the prothrombin level reached by 24 to 36 hours. This increased dosage raised slightly (from 70 to 84%) the number who reached a satisfactory prothrombin time at the end of 48 hours.

In the third series of 59 patients the initial dose of phenylpropyl-hydroxycoumarin was increased to 30 mg. with, as before, a second varying dose up to a maximum of 15 mg. This regime greatly increased the rapidity of action of the drug, 66% of cases attaining a therapeutic prothrombin time within 36 hours and 93% within 48 hours. However, such a large initial dose as 30 mg. sometimes results in excessively prolonged and dangerous prothrombin times. Of the 59 cases, 19 had prothrombin times of over 60 seconds on at least one occasion. It is true that in 11 of these 19 cases these prolonged prothrombin times might have been avoided with greater experience in the use of the drug, particularly in adjusting the amount of the second dose, and also by a more careful assessment of the patients' general health. In the remaining eight cases, however, these prolonged times could not have been foreseen; in fact, even with considerable experience it is not always easy to assess the requirements of anticoagulants, as there is a wide individual variation in the response to them.

In all three series, with initial doses of 21, 24, and 30 mg. respectively, approximately 10% of cases had prothrombin times above 60 seconds—a result that could not have been foreseen even with the most skilled and careful control. From this trial it appears that for most patients the best initial dose is 24 mg. Young robust patients who are not seriously ill (particularly those with no evidence of shock or heart failure) will probably tolerate larger initial doses in the region of 27 to 30 mg., but great care is needed when such large doses are used.

Excessively prolonged prothrombin times can be much reduced if it is realized that the full effect of phenylpropyl-hydroxycoumarin cannot be gauged for at least 36 to 48 hours. It is essential that the second dose be not given until the prothrombin time—taken not earlier than 24 to 36 hours after the initial dose—is known. In hospital practice most patients are usually started on anticoagulant therapy in the late afternoon or evening, and the prothrombin time is taken first thing the following morning. This means that the first prothrombin estimation represents the effect of less than 24 hours' therapy. An estimation taken less than 24 hours after starting anticoagulant treatment is usually of little value as a guide to the further doses required. It cannot be stressed too often that, to avoid dangerously high prothrombin times, the second dose must not be given before the effect of the initial dose has been properly assessed by a prothrombin estimation made not earlier than 24 to 36 hours after commencing therapy.

Maintenance Doses

The maintenance dose of phenylpropyl-hydroxycoumarin is shown in the Table. In 55 cases it lay between 1.5 and 3 mg., and in 80 between 1.5 and 4.5 mg. Eight cases

Maintenance Doses of Phenylpropyl-Hydroxycoumarin in 99 Cases

No. of Cases	Daily Maintenance Doses
8	0.75-1.5 mg.
55	1.5-3 mg.
25	3-4.5 mg.
11	4.5-6 mg.

required less than 1.5 mg. (usually 0.75 mg.), and 11 needed between 4.5 and 6 mg. In this trial it was found that frequent adjustment of the maintenance dose was necessary, especially

in the first two weeks, as the drug is so potent that an error in dosage as small as 0.5 mg. a day for a few days is sufficient to alter the prothrombin times considerably.

Guides to Dosage

In most cases the initial dose of phenylpropyl-hydroxycoumarin should be 24 mg. In young, robust, and less acutely ill patients, and with experience, it could with advantage be increased to 27–30 mg.

The second dose should never be given before the prothrombin time, taken at least 24 hours after starting treatment, is known. The amount of the second dose, which must never exceed 15 mg., depends on the prothrombin time taken at 24 to 36 hours:

(a) Prothrombin time 15 seconds or below ..	12–15 mg.
(b) " " between 16 and 20 seconds ..	9 mg.
(c) Prothrombin time between 21 and 24 seconds ..	3–6 mg.
(d) Prothrombin time 25 seconds and over ..	Nil

With a phenol-saline brain extract as a source of thromboplastin a time of 13–14 seconds represents 100%; a prothrombin time of 16 to 18 seconds is approximately equivalent to 50%, and a time of 21–24 seconds to 30–25%.

On the third day of therapy—that is, 48 hours after the initial dose—if the prothrombin time is 35 seconds or over, phenylpropyl-hydroxycoumarin should not be given. So long as the prothrombin time on the fourth and subsequent days is still rising no further therapy should be given. Once the prothrombin time is stationary or falling, a maintenance dose within the range of 0.75–6 mg. will be needed. If, on the other hand, the prothrombin time on the third day is below 35 seconds a maintenance dose will be required.

The first four or five days of therapy are all-important if a safe therapeutic prothrombin time is to be attained as rapidly as possible and at the same time a prolonged and dangerous prothrombin time avoided. Detailed and careful attention is needed for each patient.

Within the range of maintenance doses of 0.75–6 mg. of phenylpropyl-hydroxycoumarin there are several factors which, taken in conjunction with the prothrombin time, can help in gauging, with some accuracy, the amount required. These factors, which are common to all anticoagulants of the coumarin group, include age (apparent rather than real), weight, severity of the illness (especially whether shock or heart failure is present), liver function, and, particularly, renal function. All these factors have been discussed in detail in a previous article (Toohey, 1953).

Toxic Effects

The only toxic effect observed in the 104 cases was haematuria in five—microscopic in four and frank in one. In two of these cases, including the one with macroscopic haematuria, there was, as is not unusual, a gross urinary infection, and the haematuria was not associated with an excessively prolonged prothrombin time. In another two of the cases haematuria was present on one occasion only.

Antidote.—As reported elsewhere (Toohey, 1954) vitamin K₁ is an extremely effective and rapid antidote to over-dosage with phenylpropyl-hydroxycoumarin. Only small doses of 5–15 mg. are necessary in most cases, but owing to the marked cumulative action of the drug repeated small doses may be required when the prothrombin time is considerably prolonged (over 90 seconds). Vitamin K₁ is rapidly effective even when given by mouth, and only in frank severe bleeding with marked prolongation of the prothrombin time is parenteral treatment necessary.

Frequency of Prothrombin Estimations

With long-acting cumulative anticoagulants, such as phenylpropyl-hydroxycoumarin, it is essential that prothrombin estimations be made daily for the first six to seven days. Once the prothrombin time has become reason-

ably stable on the maintenance dose, the number of prothrombin estimations can be reduced to three a week. It is probably unwise to carry out prothrombin estimations less often than three times a week for the first three weeks of therapy, as even the smallest excess of phenylpropyl-hydroxycoumarin can, over a few days, lead to a markedly prolonged prothrombin time.

One reason given in favour of the use of the long-acting as opposed to the short-acting anticoagulants is that, once the prothrombin time is stabilized, fluctuations are much less likely to occur. This is true so long as the *exact* daily requirements of the anticoagulant are known, but in practice it is not always easy to ascertain this. The day-to-day dose of all anticoagulants varies with changes in the patient's general health. Even a slight deterioration in health may necessitate a significant reduction in the maintenance dose. Conversely, when the patient's health improves an increase in the maintenance dose is often necessary. These changing requirements, which are particularly likely to develop in patients with severe illnesses, make it difficult in many cases to assess an exact and stable maintenance dose; therefore there should be a wide enough margin of dosage to allow for changing conditions. It must be repeated that even a very small excess in the maintenance dose over a few days can lead to excessively prolonged prothrombin times.

Comparison Between Phenylpropyl-Hydroxycoumarin and Other Anticoagulants

There is not, as yet, and probably never will be, an ideal anticoagulant with a constant predictable action with a given dose. This is because, as just mentioned, even minor changes in the patient's health can significantly alter the amount of anticoagulant required. From this trial in 104 cases phenylpropyl-hydroxycoumarin was found to have no toxic side-effects. Like most long-acting anticoagulants, it has a comparatively slow action unless given in large doses. It is probably better than dicoumarol, because the incidence of haemorrhage is lower with it, and it is as quick as dicoumarol or slightly quicker in action, and also has a much more prolonged effect.

Phenindione has a definite advantage over phenylpropyl-hydroxycoumarin in its more rapid effect; also, the prolonged cumulative action of phenylpropyl-hydroxycoumarin does not occur with phenindione. However, with skilled control and reliable prothrombin estimations, a prolonged cumulative action is not such a grave drawback nowadays because there is available in vitamin K₁ a powerful and rapid antidote. Much more important qualities in a good anticoagulant are its rapidity of action and, above all, reasonably predictable results with a given dose. Lack of a uniform response, with marked variation in individual susceptibility, is the greatest drawback with any anticoagulant. In this trial, the variation in individual reactions to phenylpropyl-hydroxycoumarin was on the whole greater than with phenindione. It was found that a fairly wide range of dosage was required, and, in addition, fairly frequent adjustment of the maintenance dose was necessary.

Summary and Conclusions

Phenylpropyl-hydroxycoumarin has been tried as an anticoagulant in 104 patients, mostly cases of coronary thrombosis and phlebothrombosis. It is a most potent anticoagulant, and in safe therapeutic doses will raise the prothrombin time to within a therapeutic range in 48 hours in 84% of cases. It has a very prolonged cumulative effect and it may take as long as 7 to 14 days for the prothrombin time to return to near normal limits. In most cases, however, there is usually a significant fall in the prothrombin time from four to five days after cessation of therapy.

For most cases the initial dose should be 24 mg. and no further therapy be given until the prothrombin time

24 to 36 hours after starting treatment is known. On no account should a second dose of phenylpropyl-hydroxycoumarin be given on the result of a prothrombin estimation taken less than 24 hours after the initial dose.

In young, robust, and not acutely ill patients, increasing the initial dose to 27 or 30 mg. may be justified. Such a large dose, however, should be given only when prothrombin estimations can be done at a moment's notice at all times.

According to the prothrombin time at 24 to 36 hours, the second dose will be as follows: (a) Prothrombin time 15 seconds or below, 12 to 15 mg.; (b) prothrombin time between 16 and 20 seconds, 9 mg.; (c) prothrombin time between 21 and 24 seconds, 3 to 6 mg.; (d) prothrombin time 25 seconds and over, nil.

The maintenance dose of phenylpropyl-hydroxycoumarin will vary between 0.75 and 6 mg. In 80 out of 99 cases the maintenance dose lay within the range of 3 to 4.5 mg. Great care is necessary in assessing the maintenance dose, for even so small an excess as 0.5 mg. over a period of a few days may lead to a dangerous rise in the prothrombin time. Owing to the prolonged cumulative effect of phenylpropyl-hydroxycoumarin it may take several days before the effect of any change in dosage is apparent. Therefore, if possible, alterations in the maintenance dose should not be made more often than every few days.

Important factors in assessing the maintenance dose within the range of 0.75 to 6 mg. are the age (apparent rather than real), general health, weight, and liver and renal function. The young, robust, and less acutely ill patients require the largest doses, whilst the elderly, frail, and seriously ill patients need the smallest doses. Any lowering of renal function—for example, raised blood urea—will materially reduce the amount of the maintenance dose needed.

Frequent prothrombin estimations are necessary in controlling phenylpropyl-hydroxycoumarin therapy.

Phenylpropyl-hydroxycoumarin appears to be particularly free from toxic effects, and in this series of 104 cases the only adverse reactions were microscopic haematuria in four cases and frank haematuria in one case. This case of frank haematuria, however, was associated with a urinary infection and was not accompanied by a very marked rise of the prothrombin time.

When all possible factors, including daily prothrombin times, were taken into account, it was found that there was an unforeseen and unpredictable rise in the prothrombin time to over 60 seconds in 10% of cases.

Vitamin K₁ is a rapid and effective antidote to the action of phenylpropyl-hydroxycoumarin. Repeated doses may be necessary.

Phenylpropyl-hydroxycoumarin appears to be slightly quicker in action than dicoumarol and also less toxic. However, it is slower in action than phenindione and the variation of response to a given dose is greater. This less uniform response to phenylpropyl-hydroxycoumarin makes it more difficult to control than phenindione. Also, as it is a much more potent and cumulative drug, any inaccuracy in assessing the dose will have a much more serious effect. However, in the small number of cases where anticoagulant therapy with phenindione is difficult to control, phenylpropyl-hydroxycoumarin appears to be a useful alternative.

The total dose of phenylpropyl-hydroxycoumarin in each case was given in a single dose, daily or on alternate days, as required.

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REFERENCES

- Bourgain, R., Todd, M., Herzig, L., and Wright, R. S. (1954). *Circulation*, **10**, 680.
 Hartert, H., and Hartert, I. (1953). *Klin. Wschr.*, **31**, 852.
 Jürgens, R. (1953). *Schweiz. med. Wschr.*, **83**, 471.
 Koller, F., and Jakob, H. (1953). *Ibid.*, **83**, 476.
 Matis, P. (1953). *Aerzt. Forsch.*, **7**, Part 1, 298.
 Sailer, S., and Kresbach, E. (1955). *Wien. med. Wschr.*, **105**, 35.
 Toohy, M. (1953). *British Medical Journal*, **1**, 650.
 — (1954). *Ibid.*, **1**, 1020.

ANTICOAGULANT THERAPY IN IDIOPATHIC OCCLUSION OF THE AXILLARY VEIN

BY

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Idiopathic, or "stress," occlusion of the axillary vein is a condition that occurs in a small number of people, usually after a sudden or unusual effort. The disease was first described by Sir James Paget in 1866, and again by von Schroetter in 1884, and has recently been known under the eponym of the Paget-Schroetter syndrome. Since the original papers, accounts have appeared sporadically in the literature, and about 400 cases have been described. An excellent review of the subject was given by Hughes (1949).

The present paper reports 12 further examples of this condition, all treated with anticoagulants, and reviews the recent literature with particular reference to the value of anticoagulants in this disease.

Method of Treatment

Those patients who were admitted to hospital were given combined treatment with heparin and an anti-prothrombin agent—ethyl biscoumacetate or phenindione—according to the method already described (Marks *et al.*, 1954). Heparin was injected intramuscularly with hyaluronidase every four hours for the first twenty-four hours. The initial dose of the antiprothrombin agent was given at the same time as the first dose of heparin. Subsequent daily doses of the antiprothrombin drug were given to maintain the patient's "prothrombin content" at 10–25% of the normal as determined by the Quick one-stage method.

Patients who were not admitted to hospital were treated with either ethyl biscoumacetate or phenindione, but no heparin.

Results

The results that have been achieved by the use of anticoagulant therapy in 12 cases of occlusion of the axillary vein are compared with 19 cases collected from the recent literature (Table I). A few other reported cases have been omitted because the data were too fragmentary, because other treatment was given at the same time, or because the diagnosis was in doubt.

More detailed reports on the twelve cases are given below.

Case 1.—A fit man of 30, a painter, spent the whole of one day scraping a ceiling. That evening he experienced discomfort in the upper part of the right arm, but noticed