CLINICAL EXPERIENCE WITH WARFARIN SODIUM

BY

M. TOOHEY, M.D., M.R.C.P., D.C.H.
Physician, New End Hospital, London

Several reports (Shapiro, 1953; Wolff *et al.*, 1953; Pollock, 1955) are now available on the use of the anticoagulant warfarin sodium ("coumadin" sodium), and all are very favourable. Indeed, it has been stated that warfarin sodium is the "anticoagulant of choice" (Shapiro, 1956). This paper records the results of using warfarin sodium in 175 patients, most of whom had cardiovascular disease (myocardial infarction or cardiac failure) and the remainder phlebothrombosis and pulmonary embolism. Treatment was controlled by the simultaneous use of Quick's and Owren's "P and P" methods. A therapeutic level of between two and three times the normal control time (ideally two and a half times) was maintained when assessing results by Quick's method. For Owren's technique a level of between 10 and 14% was aimed at. This percentage prothrombin concentration is lower than that advised by Owren—10 to 30%—but I believe that a lower proportion than 30% is desirable, as I have seen fresh thrombo-embolic episodes develop between levels of 20 and 30%.

The same thromboplastin was used for both Quick's and Owren's methods—that is, a saline extraction of human brain stored at −20° C., where it keeps stable indefinitely. The Quick prothrombin time with pooled plasma from normal controls was 11 to 12 seconds with this thromboplastin.

Initial Dosage

Warfarin sodium is a unique coumarin compound in that it can be given intravenously as well as by mouth. The initial dose was given intravenously to 32 patients and orally to 143. No appreciable difference in rapidity of action was noted between the intravenous and the oral administration; therefore, except for exceptional circumstances—for example, persistent vomiting—the oral route was preferable. The usually recommended initial dose of 60 to 75 mg. was given to the first 42 patients treated. This dose, however, in nearly all instances led to a pronounced rise in the prothrombin time to above the upper limit (three times the normal control time) for therapeutic control. Small doses of vitamin K_1 had to be given to six patients to bring the prothrombin time down to a safe level. For the remaining 133 patients the initial dose was therefore sharply reduced to between 35 and 50 mg., and the latter dose was never exceeded. With these lower doses the results were much more satisfactory and made the whole control of the treatment much easier.

If too big an initial dose of most coumarin-type anticoagulants is given the peak effect of the drug may be delayed for several days and a sustained effect will still be present for many days thereafter, during which time no further dose of the anticoagulant must be given. This sustained effect is obtained even with the shorter-acting drugs such as warfarin sodium and phenindione, because to some extent sustained action depends on dosage; the larger the dose the longer the effect. If too big an initial dose is given, with the resultant marked sustained effect, it takes much longer to arrive at the correct daily maintenance dose necessary to maintain a steady prothrombin time. By keeping the initial dose to the minimum effective amount, the first maintenance dose can usually be given on the third day of treatment (about 36 to 48 hours after starting therapy). Also, by avoiding the pronounced sustained effect of too large an initial dose, the early maintenance doses will give a good approximate indication of the correct subsequent doses necessary to maintain a steady prothrombin level throughout the course of anticoagulant treatment.

Very satisfactory results were obtained with the following initial dosages of warfarin sodium: doses of 35–40 mg. were never exceeded for patients over the age of 75 years; doses of 42–50 mg. were given to all patients under 75 years. The smaller doses were given to the frailer and more seriously ill patients. An initial dose of more than 50 mg. is not advised.

The first prothrombin time was taken routinely on the morning of the third day after starting treatment (usually 36 hours after the initial dose), by which time the maximum effect of the initial dose was apparent in most patients.

Rapidity and Duration of Action

With initial doses of 35 to 50 mg. a therapeutic prothrombin time was reached in 36 hours in 95% of cases, whilst a noticeable effect on the prothrombin time was achieved in about 18 hours in most instances. The effect of daily maintenance doses of a size sufficient to maintain an adequate therapeutic level usually lasts for 36 hours. If large doses of warfarin are given, however, there is a pronounced sustained effect and the prothrombin times may remain high for much longer than 36 hours, and often for three to four days.

Warfarin sodium is therefore a rapidly acting drug with a moderately short-lasting action if large doses are avoided. In rapidity of action and duration of effect it is remarkably similar to phenindione and can be classed with that drug as a short-acting anticoagulant, in contrast to the long-acting drugs such as diphenadione ("dipaxin"), dicoumarol, and phenylpropylhydroxycoumarin ("marcoumar"). However, if large doses are given it has a much more pronounced sustained effect than phenindione.

Maintenance Therapy

It was possible to arrive at a very accurate assessment of the daily maintenance dose of warfarin sodium (to within 3 to 5%) in 158 patients (see Table). The average daily maintenance dose for all patients was 9 mg. In 68% the maintenance dose was between 5 and 12 mg., and in only 20% was the maintenance dose outside the range of 5 to 15 mg.

Maintenance Doses of Warfarin Sodium in 158 Patients

Dose	No. of Patients
2 to 5 mg.	20
5 to 12 mg.	107
12 to 15 mg.	19
15+ mg.	12

Overall average=9 mg.

The first maintenance dose was usually given on the third day of treatment. The following scheme provided a good average indication of the first maintenance doses to be given:

Prothrombin time over 3 times the normal (or below 7% by Owren's method)	Nil
Prothrombin time 2½ to 3 times the normal (7 to 9% by Owren's method)	3 to 5 mg.
Prothrombin time 2 to 2½ times the normal (9 to 15% by Owren's method)	4.5 to 10.5 mg.
Prothrombin time 1½ to 2 times the normal (15 to 20% by Owren's method)	10.5 to 15 mg.
Prothrombin time less than 1½ times the normal (above 20% by Owren's method)	15 to 20 mg.

Warfarin sodium acts rapidly enough for any appreciable change in dosage to be quickly reflected in the prothrombin times. The great advantage of rapidly acting drugs, such as warfarin sodium and phenindione, over the long-acting drugs for the treatment of acute thrombo-embolic episodes is that rapid and large changes in dosage can be quickly made, with the result that the correct maintenance dose can be rapidly determined. In the first few days of anticoagulant

therapy, because of the great individual variation in response to all anticoagulant drugs, it is impossible to know whether the patient will need small or large maintenance doses. Regulation of dose has therefore to be by trial and error guided by the results of the blood tests. Thus it is a great advantage to use an anticoagulant whose action is rapid enough for any material change in dosage to be reflected in the prothrombin times the following day.

After the first few doses of maintenance therapy, and once the prothrombin time is in the required therapeutic range, it is rarely necessary to alter the daily maintenance dose of warfarin sodium by more than 1.5 to 2 mg. When the prothrombin time has been steady for three or four days it should be realized that a change in the daily dose of more than 0.5 mg. will lead after a few days to considerable fluctuations in the prothrombin times, owing to the cumulative effect of the drug. Once the approximate daily maintenance dose has been ascertained and the prothrombin times have been steady for three or four days, a good approximate guide to any further changes in the maintenance dose which may be necessary to maintain a steady unfluctuating prothrombin time is not to alter the amount of the dose by more than 5%.

To determine the appropriate small variations in dose at this stage, bearing in mind the cumulative effect of anticoagulants, it is essential not just to consider the effect of a single dose on the prothrombin time the following day. A much clearer picture of the exact daily maintenance requirements of any anticoagulant will be obtained if the treatment is assessed over, say, a three-day period. By taking such a three-day period the full cumulative effect of small changes in dosage in the region of 5 to 10% can be readily seen and the exact daily maintenance requirements easily ascertained with a minimum of blood tests.

Ease of Control

Warfarin sodium is a remarkably easy drug to control, as the response to a given dose can almost invariably be reliably predicted. In this trial 25-mg., 10-mg., 5-mg., and 3-mg. tablets were made available. The 25-mg. tablet was used for initial dosage and the 10-mg., 5-mg., and 3-mg. tablets for maintenance therapy. For the initial doses of 35 to 50 mg. advised here, the 25-mg. tablet is unnecessary. To prescribe small variations in dose of the order of 5% the strength of tablet available is, however, of great importance. Indeed, to-day, with several good anticoagulants available, what makes one anticoagulant much easier to control than another is often the ease and convenience with which very small variations in dose may be prescribed.

The overall average maintenance dose of warfarin sodium is about 9 mg. and a 5% variation of this amount about 0.5 mg. In assessing the exact daily requirements, as mentioned earlier, it is essential to take a three-day period so that the full cumulative effect of the drug on the prothrombin times can be taken into account. For warfarin sodium one-half of a 3-mg. tablet, more or less, each three-day period, would give the necessary 0.5-mg. variation a day. A tablet strength exceeding 3 mg. makes it much more difficult to prescribe small variations in dose. To cater for initial doses of 35 to 50 mg., and for those patients who need daily maintenance doses of 12 mg. or more, a second tablet of 5 to 6 mg. or so is necessary. With two such strengths of tablet (3 mg. and 5 mg.) accurate assessment of dosage can be quickly and easily made. For long-term therapy a tablet strength of approximately 3 mg. is essential.

Conclusions

Warfarin sodium was used in the treatment of 175 patients with thrombo-embolic diseases. It is a rapidly acting drug, and 95% of all patients reached a therapeutic prothrombin time in 36 hours. With daily doses of the drug just sufficient to maintain a therapeutic prothrombin time the duration of action is approximately 36 hours. However, in large doses warfarin sodium has a very sustained effect, with a duration of action up to four to five days. It is important, therefore, to avoid large doses. The usually recommended initial dose of 60 to 75 mg. proved far too much in this series; 35 to 50-mg. doses proved perfectly adequate for initial therapy, and it is inadvisable to exceed 50 mg. as an initial dose. The overall average maintenance dose was 9 mg., and 80% of all patients were maintained on daily doses between 5 and 15 mg.

Warfarin sodium proved extremely easy to control, and it probably ranks with phenindione as one of the two best anticoagulant drugs available for short-term therapy. Initial experience with warfarin sodium shows that it is also a very useful anticoagulant for long-term therapy. Great care must be taken in prescribing the anticoagulant to allow for the very definite cumulative effect of the drug. In this respect warfarin sodium resembles in its action that of phenylpropylhydroxycoumarin, which has proved a very reliable anticoagulant for long-term therapy.

To obtain the best results with warfarin sodium it is necessary to have available a strength of tablet with which to prescribe variations in dose of 0.5 mg. easily and quickly. It is considered that scored 3- and 5-mg. tablets would be ideal.

Thanks are due to Dr. Samuel M. Gordon, of Endo Laboratories Inc., New York, for his most helpful advice and for making available the various strengths of coumadin tablets which I have used, and also to Evans Medical Supplies Ltd. for supplying warfarin sodium ("marevan") in 3 mg. and 5 mg. strengths.

REFERENCES

Pollock, B. E. (1955). *J. Amer. med. Ass.*, **159**, 1094.
Shapiro, S. (1953). *Angiology*, **4**, 380.
—— (1956). *Brit. med. J.*, **1**, 1301.
Wolff, J. M., Barker, N. W., Gifford, R. W., and Mann, F. D. (1953). *Proc. Mayo Clin.*, **28**, 489.

STAPHYLOCOCCUS AUREUS TYPE 80 AND HUMAN INFECTIONS IN UGANDA

BY

R. S. F. HENNESSEY, C.M.G., M.D., F.R.C.P.I.
Dip. Bact.

AND

R. A. MILES, A.M.I.L.T.
Wellcome Laboratories of Tropical Medicine, London

The differentiation of cultures of staphylococci by phage-typing has contributed notably towards an understanding of the epidemiology of staphylococcal disease. As well as being of value in tracing infections to particular sources, the method has provided useful information about the distribution and spread of strains of different phage types. Studies of strains isolated from healthy persons and hospital patients have shown that some phage types occur more frequently than others in certain environments, while an association between phage type and antibiotic resistance has been widely observed.

The high prevalence of antibiotic-resistant strains of phage group III in hospital infections is of special clinical interest (Blair and Carr, 1953; Rountree, 1953; Jackson, Dowling, and Lepper, 1954; Knight and Holzer, 1954). Again, some phage types seem to spread readily, while others are associated with infections possessing distinctive features. Examples of these tendencies are the recovery of type 52A strains from