Studies on Coumarin Anticoagulant Drugs

Initiation of Warfarin Therapy Without a Loading Dose

By ROBERT A. O'REILLY, M.D., AND PAUL M. AGGELER, M.D.

SUMMARY
Thirty normal subjects were given a single loading dose of warfarin sodium, 1.5 mg/kg of body weight. The drug was metabolized slowly (mean biological half-life, 47 hr) and showed a prolonged biological effect (over 6 days). In two separate experiments no loading dose was given; instead, daily doses of 15 mg and 10 mg were administered to 15 of the subjects. The prothrombin complex responses were compared with those obtained in the same subjects after the large loading dose. The mean time in days to reach the therapeutic range (prothrombin complex activity <35% of normal) was 1.1 days with the dose of 1.5 mg/kg of body weight, 2.7 days with the dose of 15 mg/day, and 5.2 days with 10 mg/day. With all three methods the therapeutic range was reached soon after a level of warfarin of 2 mg/L plasma was attained.

The rates of fall of the four vitamin K-dependent clotting factors (II, VII, IX, and X) with the large loading dose and with the daily dosage of 15 mg were compared in six of the subjects. With the loading dose, factor VII activity was less during the first 48 hr, but there was no other significant difference between the two methods of drug administration in the amount of reduction of any of the four factors.

Since the role of factor VII in thrombogenesis is questioned, these results provide a rational basis for the induction of prophylactic anticoagulant therapy without large loading doses of warfarin. Avoidance of the customary loading dose should reduce the danger of hemorrhage, particularly in patients who are sensitive to the drug because of advanced age, sepsis, liver disease, congestive heart failure, or recent surgery or trauma.

Additional Indexing Words:
Hemorrhage   Blood coagulation   Blood coagulation factors   Prothrombin

THERAPY with oral anticoagulant drugs is usually initiated with a large loading dose; the size of subsequent daily doses is adjusted according to prothrombin test responses until a stable maintenance level is reached.1 The large initial dose is used to produce the greatest anticoagulant effect in the shortest time possible. However, this method of initiating therapy may lead to an excessive and dangerous degree of anticoagulation in some patients. The rapid absorption and slow metabolism of warfarin sodium and the prolonged biological effect from a single dose suggested to us that drug levels adequate for therapeutic response could be achieved without a large loading dose.2 3 We have therefore studied the effect of initiating treatment with daily doses only slightly larger than the anticipated maintenance dose. This method minimizes the danger of excessive anticoagulation yet delays the development of the therapeutic effect only slightly if at all.

Methods
Thirty normal men and women, 21 to 63 years of age, were studied. A single large loading dose of warfarin sodium, 1.5 mg/kg of body weight, was administered orally to all 30 subjects. In two separate experiments no loading dose was given
to 15 of the subjects. Instead, in one experiment all subjects received 10 mg/day orally, throughout the period of observation except N-2, whose dosage was reduced to 5 mg/day at 96 hours. In the other experiment all subjects received 15 mg/day orally, throughout the period of observation except N-2, whose dosage was reduced to 5 mg/day at 72 hours. Three or more weeks were allowed between experiments, and in all subjects the one-stage prothrombin time had returned to normal before a new experiment was started.

Prothrombin times were determined serially. In six patients the responses of clotting factors II, VII, IX, and X after administration of the single loading dose of warfarin were compared with the responses during use of the daily dosage of 15 mg.

The methods used for administering the warfarin sodium, for collecting and processing the test specimens, and for determining the concentration of warfarin in plasma have been described previously. The plasma prothrombin complex activity was determined by the one-stage prothrombin time of Quick,† using a saline dilution curve. Specific clotting factors were measured as follows: factor II (prothrombin) by the method of Owren and Aas, factor VII (proconvertin) by the method of Owren and Aas with the use of congenital proconvertin-deficient plasma, factor

### Table 1

**Plasma Warfarin Concentrations in Thirty Normal Subjects after a Single Loading Dose***

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*1.5 mg/kg of body weight.

*Kindly supplied by the late Dr. Nathan Weiner of Endo Laboratories, Garden City, New York.

†The diagnostic plasma used in standardizing the plasma prothrombin time curves was kindly supplied by the Warner-Chilcott Laboratories, Los Angeles, California.
IX (plasma thromboplastin component, P.T.C.) by the method of Kropatkin and associates,\textsuperscript{5} and factor X (Stuart-Prower) by the method of Bachmann and associates.\textsuperscript{6}

**Results**

The results following administration of the single large loading dose are shown in tables 1 and 2. We previously showed that this dose, which is larger than the usual loading dose, lengthens the one-stage prothrombin time at the fastest possible rate.\textsuperscript{3} The mean plasma warfarin concentration at 24 hr was 8.8 mg/L and the mean half-life of drug in plasma was 47 hr. The plasma concentration of warfarin remained above 2 mg/L for over 120 hr. In all cases the prothrombin complex activity was significantly reduced by 24 hr, was well within the “therapeutic range” (<35% of normal) by 36 hr, and reached a maximum reduction between 36 and 96 hr. The mean reduction in prothrombin complex activity was maximum at 48 hr and remained within the therapeutic range through the 120-hr period of observation.

The warfarin concentrations in plasma and the effects on the prothrombin complex activity in the experiments in which no loading dose was administered are reported in tables

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**Table 2**

Prothrombin Complex Response in Thirty Normal Subjects after a Single Loading Dose of Warfarin\textsuperscript{*}

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\textsuperscript{*}1.5 mg/kg of body weight.

\textsuperscript{1}Subject took 10 mg of vitamin K\textsubscript{1} orally at this time.
Table 3

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<td>N-22</td>
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<tr>
<td>N-31</td>
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<td>N-32</td>
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| Mean | 0.9 | 1.3 | 1.7 | 2.0 | 2.2 | 0.8 | 1.8 | 3.0 | 2.4 | 2.0 |

| sd | ±0.4 | ±0.4 | ±0.5 | ±0.4 | ±0.6 | ±0.8 | ±0.4 | ±0.5 | ±0.7 | ±1.1 | ±1.2 |

*Dose reduced to 5 mg/day at 96 hr.
†Dose reduced to 5 mg/day at 72 hr.

O'REILLY, AGGELER

The means of the plasma drug concentrations and prothrombin complex activity responses obtained with the three dosages are shown in Figure 1.

The rates of fall of the four vitamin K-dependent clotting factors (II, VII, IX, and X) after the loading dose and during the daily dosage of 15 mg were compared in six of the subjects. The percentage value that each factor was reduced from its pretreatment value (taken as 100%) is given in Table 3. The only factor which showed a significant difference was factor VII; at 24 hours the mean reduction was 83% with the loading dose and 44% without it (P < 0.01) and at 48 hours the mean reduction was 95% with the loading dose and 88% without it (P < 0.05). The difference in the amount of reduction was no longer significant at 72, 96, and 120 hr. A comparison of the effect of the two methods of initiating therapy on the concentration of the vitamin

3 and 4, respectively. With the 10 mg/day dosage the mean level of drug in plasma gradually rose to 2.2 mg/L by 120 hr, and with the 15 mg/day dosage it rose to 3.1 mg/L by 72 hr. With the 10-mg dosage the mean prothrombin complex activity gradually fell to 32% of normal at 144 hr. The therapeutic range was reached between 48 and 144 hr in all but one case. With the 15-mg dosage the prothrombin complex activity gradually fell to 28% of normal by 96 hr. The therapeutic range was reached between 24 and 96 hr in all cases.

Circulation, Volume XXXVIII, July 1968
Table 4
Prothrombin Complex Response in Fifteen Normal Subjects Given Small Daily Doses of Warfarin Sodium Without a Loading Dose

<table>
<thead>
<tr>
<th>Subject</th>
<th>0 hr</th>
<th>24 hr</th>
<th>48 hr</th>
<th>72 hr</th>
<th>96 hr</th>
<th>120 hr</th>
<th>144 hr</th>
<th>168 hr</th>
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<td>32</td>
<td>22</td>
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<tr>
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<td>43</td>
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<td>67</td>
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<tr>
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<tr>
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Daily Dosage of 10 mg of Warfarin Sodium

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<tr>
<th>Subject</th>
<th>0 hr</th>
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<th>48 hr</th>
<th>72 hr</th>
<th>96 hr</th>
<th>120 hr</th>
<th>144 hr</th>
<th>168 hr</th>
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<td>±10</td>
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</table>

* Dose reduced to 5 mg/day at 96 hr.
† Dose reduced to 5 mg/day at 72 hr.

K-dependent clotting factors in one subject (N-27) is shown in figure 2.

In hospitalized patients treated with a starting dose of 15 mg/day we found that the time required to reach the therapeutic range correlated roughly with the ultimate daily dose required to maintain prothrombin complex activity within the therapeutic range. When the time was 2 days or less, the required maintenance dose was usually 5 mg or less. When it was 2 to 3 days, the dose was usually about 7.5 mg, and when it was 4 days or longer, a dose of 10 mg or more was usually required.

**Discussion**

The synthesis of clotting factors II, VII, IX, and X requires vitamin K; under the influence of coumarin drugs, production of these factors ceases. The consequent lengthening of the
Comparison of Mean Clotting Factor Responses to a Single Large Loading Dose and to Small Daily Doses of Sodium Warfarin in Six Normal Subjects

<table>
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<th>Clotting factor</th>
<th>Method</th>
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<tr>
<td></td>
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<td>0 hr</td>
</tr>
<tr>
<td>II</td>
<td>Large loading dose†</td>
<td>0 22±11</td>
</tr>
<tr>
<td></td>
<td>Small daily dose‡</td>
<td>0 24±11</td>
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<tr>
<td>VII</td>
<td>Large loading dose§</td>
<td>0 83±17</td>
</tr>
<tr>
<td></td>
<td>Small daily dose</td>
<td>0 44±18</td>
</tr>
<tr>
<td>IX</td>
<td>Large loading dose</td>
<td>0 44±19</td>
</tr>
<tr>
<td></td>
<td>Small daily dose</td>
<td>0 40±13</td>
</tr>
<tr>
<td>X</td>
<td>Large loading dose</td>
<td>0 28±15</td>
</tr>
<tr>
<td></td>
<td>Small daily dose</td>
<td>0 23±10</td>
</tr>
</tbody>
</table>

*Results are expressed as mean ± standard deviation.
†1.5 mg of drug/kg of body weight.
‡15 mg of drug every day except in one subject whose dose was reduced to 5 mg/day at 72 hours.
§Difference between the paired means significant at P < 0.01.
‖Difference between the paired means significant at P < 0.05.

Figure 2

Comparison of loading dose (120 mg) and no loading dose (15 mg/day) methods of initiating anticoagulant therapy with warfarin sodium. The effect on the concentration of factors II, VII, IX, and X in subject N-27 are shown.

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length of time that the drug will remain in
the plasma in a concentration above the level
required for the suppression of new clotting
factor production. The longer the drug is
present above this level, the greater is the
degree and the duration of response. No sig-
nificant difference in the inherent ability of
the various coumarin and indanedione anti-
coagulant drugs to produce this maximum
rate response has been noted.12 The degree
and duration of response, however, vary with
the rate of absorption and the metabolic half-
life of the drug: compounds that are absorbed
and disappear rapidly from the blood pro-
duce a lesser maximum degree of clotting fac-
tor depression and a faster return to normal;
drugs that are absorbed and disappear at
slower rates have a longer time to act and
hence produce a greater maximum degree of
clotting factor depression and a slower return
to normal.13

It is customary to use large loading doses
of the oral anticoagulant drugs to produce a
rapid prolongation of the prothrombin time.
When warfarin sodium was introduced into
clinical therapeutics, the recommended initial
loading dose was about 1 mg/kg of body
weight. This amount of warfarin represents a
more potent dose than the usual loading dose
of 300 mg of dicumarol; this, rather than any
inherent difference between the drugs, is
probably responsible for the more rapid onset
of the effect of warfarin than of dicumarol in
clinical practice.7, 13

An occasional patient with a normal func-
tioning hemostatic mechanism and many pa-
tients who have recently undergone major
surgery or are elderly, septic, malnourished,
debilitated, or suffer from liver disease or
congestive heart failure respond excessively
to a loading dose of 1 mg of warfarin/kg of
body weight. The principal advantage of
initiating therapy with the small daily dosage
is that there is less danger of producing an
excessive effect in a sensitive patient. This
method also avoids any marked difference
between the size of dose used to initiate
therapy and that required to maintain it.
This is desirable with such drugs as warfarin
which have long biological half-lives.

The main argument against the small daily
dosage method for initiating therapy is that
there is a delay in achieving the desired level
of prothrombin complex activity. However,
most of our subjects who received 15 mg/day
achieved a reduction to 35% or less activity
in the one-stage prothrombin test by 72 hr
and all reached this level by 96 hr. This is
sufficiently rapid for prophylactic therapy un-
der almost all circumstances.14-16 When rapid
anticoagulation is required, as in the treat-
ment of acute pulmonary embolism or deep
venous thrombosis, the immediate use of
heparin is preferred and a slight delay in
achieving the desired prothrombin complex
levels when shifting to oral anticoagulant
therapy later is of no consequence. When it
is not feasible to use heparin, the priming
dose method may be employed to achieve
early, maximum anticoagulation.

The therapeutic basis for the use of oral
anticoagulant drugs is predicated on their
interference with blood coagulation.1 The
faster onset of reduction in activity of the
prothrombin complex with large loading
doses of oral anticoagulant drugs appears to
be entirely the result of the more rapid decline
in activity of factor VII. In some instances
the release of tissue thromboplastin from
atheromatous arterial lesions may be respon-
sible for the development of thrombi.17 If
such a mechanism, which involves the ex-
trinsic system of blood coagulation,18 were
operative, the speed of reduction of factor
VII would be important. It is believed by
many investigators, however, that the coagula-
tion phase of thrombogenesis, particularly
in venous thrombosis, is mediated through the
intrinsic system of blood coagulation.1, 19
The clotting factors involved in the intrinsic
pathway that are influenced by coumarin
drugs (factors II, IX, and X) fall just as
rapidly when therapy is initiated with the
15-mg dose as when the large loading dose of
warfarin is employed.

Deykin and associates20 found that, despite
early lengthening of the one-stage prothrom-
bin time to the therapeutic range, the oral
anticoagulant drugs fail to exert antithrombotic, as opposed to anticoagulant, effects for at least 5 days. Presumably this amount of time was required to reduce clotting factors other than factor VII to a sufficient degree. Hovig and co-workers\textsuperscript{21} showed in dogs and Jørgensen and Borghervink\textsuperscript{22} in man that experimental hemostasis is not impaired by marked deficiency of factor VII. This factor is apparently not necessary for stabilization of platelet thrombi. Therefore, it seems likely that despite the delay in the rate of fall of factor VII when the large loading dose is omitted, full antithrombotic effect is achieved just as quickly as when it is used.

Our findings with warfarin are reminiscent of those reported for digoxin. Both types of drugs are eliminated from the body by first order processes.\textsuperscript{3, 23, 24} Marcus and associates recently reported that the blood levels of digoxin in man\textsuperscript{24} and the blood and tissue levels of digoxin in the dog\textsuperscript{25} were the same by the end of 6 days whether therapy was initiated with or without a loading dose. It appears that drugs like warfarin and digoxin, which have very long biological half-lives, will accumulate sufficiently in the blood for therapeutic effect when given daily without a loading dose.

References


COUMARIN ANTICOAGULANT DRUGS

Studies on Coumarin Anticoagulant Drugs: Initiation of Warfarin Therapy Without a Loading Dose

ROBERT A. O'REILLY and PAUL M. AGGELER

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