A Nomogram for Long-Term Anticoagulant Therapy

By William R. Tench, M.D., and Hugh C. Ross, B.S.

The routine use of anticoagulants on an ambulant basis is modified by many variables. Among these are bleeding tendencies, renal and hepatic disease pre-existing or developing during such therapy, and complications of the primary disease. Increased sensitivity to anticoagulants enhanced by minor alcohol excesses and other medications may be further imbalanced by memory defects or excessive compulsions. These variables are carefully weighed in the decision to initiate this therapy. But even in their absence the problem of recommending predictable dose schedules tends to be resolved by the trial and error of experience. Physicians who are not primarily interested in this therapy tend to shy away often when it is sorely indicated. The purpose of this report is to present a means for the management of long-term anticoagulant therapy.

The basis for this presentation has been the management of 278 patients comprising 470 patient-years. Their course and complications are not the subject of this report. From this experience, however, a nomogram has been derived to improve the ease and efficiency of long-term anticoagulant therapy. About 200 patients initially given Dicumarol have been retained on this anticoagulant. During the past 2 years additional patients have been given Warfarin sodium. Currently 242 patients, 158 are taking Dicumarol. The remaining 84 are on Warfarin sodium. There appears to be no significant difference in the effectiveness of either anticoagulant other than a 10:1 ratio of the former over the latter for maintenance purposes. Values in the nomogram are multiplied by 10 for patients on Dicumarol. Prothrombin times have been performed by the one-stage Quick method by use of a 13-second control thromboplastin (Simplastin). When carefully performed, the reliability of this test may be indicated by the following:

1. Twenty determinations on the same normal person yielded prothrombin times from 13.7 to 14.5 seconds, with a mean value of 14.09 seconds. Standard deviation of the mean, ± 0.22 second.

2. Ten determinations on a commercial plasma (Diagnostic Plasma, Warner-Chilcott) yielded prothrombin times from 13.8 to 14.2 seconds, with a mean value of 14.03 seconds. Standard deviation of the mean, ± 0.10 second.

3. Ten determinations on a second test plasma (Standardized Normal Plasma, Dade Reagents, Inc.) yielded prothrombin times from 12.9 to 13.5 seconds, with a mean value of 13.24 seconds. Standard deviation of the mean ± 0.23 second. Initially the primary objective was to establish a patient’s specific weekly requirement for the anticoagulant. This varied from 10 mg. of Warfarin weekly, and schedules were drawn progressively, increasing by small increments to 220 mg. weekly as may be seen centered in the nomogram (fig. 1). Almost a third of these patients required less than 30 mg. weekly. Therefore to avoid early difficulties 25 mg. of Warfarin sodium are used initially in practically all patients. Five milligrams are given the second day, and a prothrombin time is performed on the third day, acutely ill patients being “covered” with heparin. The degree of sensitivity to the anticoagulant, as reflected by the first prothrombin time, has been used to indicate the approximate daily dose. Subsequent prothrombin times serve to place a patient in his particular weekly dose schedule. The schedules themselves are patterned to make it easy to memorize them.

Two years ago a chart was constructed with the left-hand vertical column representing increasing weekly doses. Opposite each weekly
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The nomogram itself.

schedule, ascending from 13 seconds to 50 seconds, were the milligrams of Warfarin required or omitted to return a given schedule to its desirable range (table 1). The original adjustments for the chart, depicted in table 1, were entirely arbitrary, modified at frequent intervals through the experience of trial and error. As more and more points were obtained yielding a satisfactory response to a given adjustment for a specific weekly dose schedule, the predictability of the chart improved. It was then noted that these incre-
Table 1

An Abbreviation of the Chart Used for the Management of Long-Term Anticoagulant Therapy for a Two-Year Period and from Which the Nomogram Was Constructed

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<th>P.T. in Seconds</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>Days omitted (Mgs. subtracted from week's usual dose)</th>
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<td>14.4</td>
<td>mg.</td>
<td></td>
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</table>

Opposite the patients usual weekly requirement of Warfarin is chosen the adjustment required beneath a given prothrombin time.

X = No change in schedule.
The right half of this chart is interpreted in days of omission of usual dose. Half days equal one half a given days dose.
In parenthesis would be milligrams corresponding to such omissions—values employed in drawing the curves in Figure 2.
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Table 2
Summary of Progressive Improvement in Managing Patient without the Chart, with the Chart, and Finally with the Nomogram

<table>
<thead>
<tr>
<th>Case</th>
<th>N</th>
<th>(\sqrt{n})</th>
<th>S</th>
<th>(\frac{1.96 \times S}{\sqrt{n}})</th>
<th>(m \pm \text{Tolerance})</th>
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</thead>
<tbody>
<tr>
<td>Seconds deviation in desired prothrombin time per number</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>.640</td>
<td>5.4 \pm .640</td>
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<td>.93</td>
<td>.318</td>
<td>1.90 \pm .318</td>
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<td>9.4</td>
<td>2.24</td>
<td>.467</td>
<td>2.3 \pm .467</td>
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<tr>
<td>Number corrections in dosage required per year</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chart</td>
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<td>6</td>
<td>4.14</td>
<td>1.36</td>
<td>15.3 \pm 1.36</td>
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<td>Nomogram</td>
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<td>4.86</td>
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<tr>
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<td>1.50</td>
<td>.945</td>
<td>8.4 \pm .945</td>
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</table>

ments or omissions followed a pattern. Curves were then drawn by plotting on the abscissa the number of milligrams required to return a patient to the desired range against the ordinate, representing the prothrombin time in seconds with progressively greater weekly doses required (fig. 2). These curves were found to follow a linear pattern when plotted on semilog paper and to conform to the equation \[ \Delta D = 8.95 \times DN \times 0.62 \times \log \left(\frac{25}{t}\right). \] \(\Delta D\) represents the adjustment necessary to return a patient to a satisfactory level and DN represents his weekly dose. As may be seen in figure 2, by adapting "the best straight line" to these curves, shortcomings in the ranges of 20 to 25 seconds (23 to 18 per cent) could be corrected. Now, either a new, more accurate chart could be composed or a more versatile instrument, such as a nomogram, could be constructed (fig. 1) with three variables.*

1. Prothrombin time in seconds (or per cent).
2. Individual dose schedule per week.
3. Varying dose schedules of the anticoagulant per patient.

A straight edge is laid from a point on the right hand vertical scale (scale B) which is determined by a prothrombin time done on the patient's usual test day. When laid across the horizontal line (scale C) at a point corresponding to his usual weekly requirement of the anticoagulant, it transects the left-hand vertical line (scale A) at a point where one may read off the number of milligrams necessary to add or subtract from his current week's dosage to restore him to the desired 24-second level on his subsequent test date, 2 to 4 weeks hence.

For example, a patient taking 50 mg. of Warfarin sodium per week, i.e., 10 mg. daily omitting Sunday and Wednesday, is found on his test day to have a prothrombin time 17 seconds. The straight edge is placed at 17 seconds on scale B and when laid across scale C at 50 mg. it is found to transect scale A at +17.5 mg. One therefore advises him to take 3½ of the 5-mg. tablets extra "today" and then to continue his usual schedule and return in 2 weeks or whatever period he has been found to require for readjustment. If his prothrombin time is 35 seconds, the straight edge is found to transect scale A at -15 mg., which would result in the advice to omit "today's" Warfarin entirely and to take only 5 mg. "tomorrow." If "tomorrow" or "today" were a "skip day," he is advised to carry out the same omissions the following days. If a prothrombin time is found to be over 45 seconds (less than 9 per cent), 5 or 10 mg. of vitamin K₁ oxide (Mephyton) are advised, prothrombin times are done at shorter intervals, and other reasons for instability are sought. Should he consistently require either

*See appendix for construction of nomogram.
An abbreviation of curves based on table 1 and their major points connected to reveal the relationship of increasing weekly dosage (DN); the required change in dose (ΔD); and the measured prothrombin time (P.T.).

Mathematical expression of construction of nomogram.

subtraction or addition of his usual dose, he is changed to a larger or smaller weekly dose schedule.

The ideal record of a patient on this therapy would reveal that in 1 year a prothrombin time every 2 weeks or 26 times in the year would not require a single adjustment, and that at no time would it vary from 24 to 30 seconds, if the thromboplastin used were controlled at 13 seconds. Thirty-six patients were found to have been observed continuously for 3 years. One year before the chart was constructed from which the nomogram is derived their records were analyzed to determine the frequency and degree that they varied from such an ideal record. Their records were again compared to a 1-year period when their management was controlled by the chart itself. To 32 (the sequence having been interrupted in four) of these same patients were added 65; they were all controlled by the nomogram alone for a 6-month period. In the management of the first group it was found that 36 patients required 659 readjustments and fell short by a total of 2,789 seconds. Each patient averaged 7.75 seconds per month below
the desired 24-second level, with a standard deviation of 2.7 second, and required an average of 18 adjustments a year, with a standard deviation of 4.3. With the aid of the chart, they required 550 readjustments but still fell short 1,952 seconds. Each patient now averaged 5.4 seconds per month, with a standard deviation of 1.96, and required 15.3 readjustments in the year, with a standard deviation of 4.14.

Under control by the nomogram, these same patients averaged 1.95 seconds low per month, with a standard deviation of 0.93, and required readjustments at a rate of only 7.2 per year, with a standard deviation of 4.86. When the additional 65 patients were incorporated within the last group, the average time a patient fell short became 2.3 seconds per month, with a standard deviation of 2.24, and required 8.4 adjustments, with a standard deviation of 1.5 for the year. As may be seen in table 2, employing the formula \( \frac{1.96 \cdot s}{\sqrt{n}} \) the improvement has been significant.

"If we take a random sample of size 'n', where N is 30 or more, and calculate \( \bar{X} \) and s of this sample, then we can assert with a probability of about .95 that \( \bar{X} \) will not differ from the true mean of the population by more than \( \frac{1.96 \cdot s}{\sqrt{n}} \)."''

Summary

It appears that the nomogram, because of its predictability, has been useful, not only in patients who tend to vary their requirements, but as a tool to find the proper weekly schedule for each patient. Moreover, prothrombin times have tended to lose their peaks and valleys; adjustments have become less frequent and of much smaller degree.

Conclusion

Experience in long-term anticoagulant therapy has served as a basis for the development of a nomogram for its management.

Reference


Circulation, Volume XXIV, September 1961

APPENDIX

Determination of Equation of Basic Data

The basic data consisting of measured prothrombin time (P.T.) vs. required change in dose (\( \Delta D \)) to return a patient to the desired prothrombin time of 25 seconds was plotted on semilog paper (t on log scale).

A separate straight-line plot of increasing slope for increasing weekly dosage (\( Dn \)) was obtained for each increment of \( Dn \) indicating the relationship

\[ \Delta D = F(Dn) \log \frac{25}{t} \]

where

\[ F(Dn) \]

was then plotted vs. \( Dn \) on log-log paper. A straight line function was obtained of the equation

\[ F(Dn) = 8.95(Dn)^{0.96} \]

Combining the above two equations, all of the information contained in the basic data can be expressed by the equation:

\[ \Delta D = 8.95 Dn^{0.96} \log \frac{25}{t} \]

Construction of Nomogram

A nomogram was constructed to provide a simple method for solving the equation:

\[ \Delta D = 8.95 (Dn)^{0.96} \log \frac{25}{t} \] (1)

The design of the nomogram was based on the geometry of figure 3 which yields the identity:

\[ b = \frac{a}{c} d \] (2)

Equating like parts of (1) and (2) yields:

\[ b = \Delta D, \frac{a}{c} = 8.95 (Dn)^{0.96}, d = \log \frac{25}{t} \] (3)

Assuming that the same number of units per inch is used for each of the parameters in (3), then the equations are solved for the values of \( \Delta D \), \( Dn \), and \( t \) and plotted to the chosen scale. In this equation the result was that either scale b was too long or d too short. This was compensated for as follows: if \( T (b) \) is the total length available for line b, and S (\( \Delta D \)) is the maximum value of \( \Delta D \) minus the minimum value, then let \( N_t = T(b)/S(\Delta D) \). Similarly, let \( N_z = T(d)/S(\log 25/t) \).

Multiplying both sides of (2) by \( N_z/N_t \):

\[ \frac{Nb}{N_t} = \frac{N_{\Delta d}}{N_t} d \]

\[ b N_t = \frac{a N_{\Delta d}}{c N_t} d N_z \] (4)

Equating (4) to (1):

\[ b = \frac{\Delta D}{N_t} \] (5)

\[ d = \frac{\log 25}{N_t} \] (6)

\[ a = c \frac{N_z}{N_t} 8.95(Dn)^{0.96} \] (7)
In (7), if \( T(ac) \) is the total length available for line \( a + c \), then \( c = T(ac) - a \). Inserting this in (7):

\[
a = \left[ T(ac) - a \right] \frac{N_2}{N_1} 8.95 \text{(DN)} \cdot 62
\]

\[
a \left[ \frac{N_1}{N_2} + 8.95 \text{(DN)} \cdot 62 \right] = T(ac) 8.95 \text{(DN)} \cdot 62
\]

\[
a = \frac{T(ac) 8.95 \text{(DN)} \cdot 62}{\frac{N_1}{N_2} + 8.95 \text{(DN)} \cdot 62}
\]

(8)

(5), (6), and (8) are then solved for the values of \( AD \), \( t \), and \( DN \). These quantities are then plotted on the specified, \( b \), \( d \), or \( (ac) \) lines with the value of \( AD \), \( t \), or \( DN \) used to calculate a particular point noted next to that point. If \( T(b) \), \( T(d) \), and \( T(ac) \) are in inches, then \( N_1 \) and \( N_2 \) will be in units/inch and \( a \), \( b \), and \( d \) will be in inches.

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The Internal Environment

Ancient science was able to conceive only the outer environment; but to establish the science of experimental biology, we must also conceive an inner environment. I believe I was the first to express this idea clearly and to insist on it, the better to explain the application of experimentation to living beings. Since the outer environment, on the other hand, infiltrates into the inner environment, knowing the latter teaches us the former's every influence. Only by passing into the inner, can the influence of the outer environment reach us, whence it follows that knowing the outer environment cannot teach us the actions born in, and proper to, the inner environment. The general cosmic environment is common to living and to inorganic bodies; but the inner environment created by an organism is special to each living being. Now, here is the true physiological environment; this it is which physiologists and physicians should study and know, for by its means they can act on the histological units which are the only effective agents in vital phenomena.—Claude Bernard, *An Introduction to the Study of Experimental Medicine*. New York, The MacMillan Company, 1927, p. 76.
A Nomogram for Long-Term Anticoagulant Therapy
WILLIAM R. TENCH and HUGH C. ROSS

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