Long-Term Treatment of Angina Pectoris with Dicumarol

By Zeth Gabrielsen, M.D.†, and Jon R. Myhre, M.D.

By the use of “report cards” the daily amount of anginal pain and the weekly consumption of nitroglycerin tablets were registered in a small series of patients during alternating courses of Dicumarol and a placebo, covering in all more than 2 years. The total number of Dicumarol periods was 24, half of them lasting more than 6 months. The effect of Dicumarol was evaluated.

During the last few years reports have appeared of the favorable therapeutic effect of anticoagulants on pain in cases of angina pectoris. Heparin at first had its advocates, but later the possibility of reducing the severity and frequency of the anginal attacks through the use of this drug has been seriously disputed. At present the use of Dicumarol and allied drugs is considered more promising. Remarkably good results from the protracted use of these drugs have been reported, and some authors have even found marked improvement after a few days of treatment. Most workers base their conclusions on personal interviews or written questionnaires issued to the patients. These and some other methods for the evaluation of drug effect on cardiac pain have been severely criticized by Greiner and associates, who emphasize the many fallacies, especially the influence of suggestion, and the necessity of adequate control material. In the present study a small group of patients with angina pectoris receiving alternately Dicumarol and a placebo has been followed for more than 2 years by the use of a technic described by Greiner and co-workers. The results do not support the claims of a beneficial effect of Dicumarol on the anginal pain.

Material and Methods

Our material comprises 10 normotensive individuals, 9 men and 1 woman, suffering from arteriosclerotic heart disease and angina pectoris (Table 1).

Four of the subjects had previously suffered from acute myocardial infarction with resulting typical and lasting electrocardiographic changes. In the other cases the resting electrocardiograms were normal, and the diagnosis was based on clinical criteria. A positive electrocardiogram after work or hypoxia presented additional diagnostic evidence, in all cases except 1 (no. X). Hypercholesterolemia (over 400 mg. per cent) was found in 3 cases, especially severe and accompanied by marked tendon xanthomata in no. VI, our youngest patient. None of the subjects suffered from congestive heart failure at the beginning of the study, but moderate failure gradually developed in case no. X. The heart size was normal in all cases except in this subject.

For registration of the anginal pain we used the “daily report cards” of Greiner and co-workers (fig. 1). The card covers 1 week and allows a grading of the separate days. To obtain from the cards a numerical expression of the patient’s condition during each whole week it was decided to use the following scale:

- A day of no cardiac pain 0
- A day of less than usual pain 1
- A day of pain as usual 2
- A day of more than usual pain 3

By adding the values for the separate days of

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From the Medical Department A, University Clinic, Bergen, Norway.
†Deceased October 27, 1957.
TABLE 1.— Pertinent Data on Ten Cases of Angina Pectoris

<table>
<thead>
<tr>
<th>Case no.</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) and sex</td>
<td>60 M</td>
<td>45 M</td>
<td>54 M</td>
<td>61 M</td>
<td>59 M</td>
<td>42 M</td>
<td>46 M</td>
<td>59 M</td>
<td>50 M</td>
<td>58 M</td>
</tr>
<tr>
<td>Hypercholesterolemia (&lt;400 mg. per cent)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Duration of angina pectoris (years)</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Previous myocardial infarct (years before study)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The week, a sum representing the whole week was obtained. The figures for each week of the total period of observation were used as a basis for the evaluation of the information gained from the report cards.

The effect of Dicumarol on the blood coagulability was tested by the prothrombin-proconvertin method of Owrern,10 11 the aim being to keep the values between 15 and 30 per cent. No episodes of bleeding or other complications of anticoagulant therapy were encountered. The prothrombin-proconvertin level was below 35 per cent during 85 per cent of the Dicumarol treatment periods.

At the initiation of the study subject no. VI had already been treated with Dicumarol for 2 weeks. The others all went through a “control period” of approximately 2 months’ duration before any tablets, except the usual nitroglycerin tablets, were administered. Thereafter Dicumarol tablets and placebo tablets were administered in alternating courses for more than 2 years in each case. Blood samples were collected regularly also during the placebo periods.

The placebo tablets were exact replicas of the drug tablets in size, appearance, and consistency, and, as far as we could judge, also in taste. They were made from starch and lactic acid and “flavored” with a little quinine.

A fresh supply of tablets was issued when the patients visited the hospital for blood coagulability control. The “daily report cards” were collected at the same time. No attempts were made to register the condition of the patients during these visits, all duties being performed by a nurse with only the most necessary information concerning the difference between the placebo tablets and the drug tablets. Conditions closely approximating the “double blind” requirements were thus obtained.

The duration and number of the different periods are apparent from figure 2. The whole study covers 8,498 patient days or 1,214 patient weeks. The “control periods” account for 7 per cent of the time, 55 per cent represents the Dicumarol periods and 38 per cent the placebo periods. The total number of Dicumarol periods is 24, of which 3 were of less than 4 months’ duration, 9 lasted between 4 and 6 months, 5 between 6 and 8 months, and 7 lasted between 8 and 11½ months.

Six subjects managed to keep count of their consumption of nitroglycerin tablets, recording on their report cards the amount of tablets used per week. In this way additional evidence for the evaluation of their condition was obtained. It might be tempting to consider the information concerning the nitroglycerin consumption as more “objective” and accordingly more valuable than the information concerning the pain. As pointed out by other workers, however, many factors other than pain influence the use of nitroglycerin tablets.

RESULTS

Our results are graphically recorded in figure 2. As might be expected, the curves for anginal pain and for nitroglycerin consumption show a rather varying course, although we have chosen not to plot the values for each single week, but have used the bi-weekly averages. One subject, no. III, died suddenly after 22 weeks of continuous Dicumarol therapy and before any placebo treatment had been administered. The clinical picture was that of an acute myocardial infarction.

The pain report curves remained at approximately the same levels during the whole period of observation. No systematic tendency could be seen toward lower curve levels at the end of the Dicumarol periods, indicating improvement, or higher levels, indicating deterioration, at the end of the placebo periods. A marked pain reduction seemed to have taken place in cases nos. VI and VIII toward the end of the first year. In case no. VI the
FIG. 2. Graphic presentation of the values for pain as calculated from the daily report cards (unbroken line) and of the values for the consumption of nitroglycerin tablets (broken line). Ordinate, scale for pain values on left and for nitroglycerin consumption on right.
TABLE 2.—Average Weekly Values for Pain and Nitroglycerin Consumption During the First and Last Four Weeks of the Dicumarol Periods and the Placebo Periods

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Dicumarol periods</th>
<th>Placebo periods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First 4 weeks</td>
<td>Last 4 weeks</td>
</tr>
<tr>
<td>I</td>
<td>Pain Ngl.</td>
<td>2.0</td>
</tr>
<tr>
<td>II</td>
<td>Pain Ngl.</td>
<td>12.7</td>
</tr>
<tr>
<td>III</td>
<td>Pain Ngl.</td>
<td>15.0</td>
</tr>
<tr>
<td>IV</td>
<td>Pain Ngl.</td>
<td>13.9</td>
</tr>
<tr>
<td>V</td>
<td>Pain Ngl.</td>
<td>10.4</td>
</tr>
<tr>
<td>VI</td>
<td>Pain Ngl.</td>
<td>9.0</td>
</tr>
<tr>
<td>VII</td>
<td>Pain Ngl.</td>
<td>7.8</td>
</tr>
<tr>
<td>VIII</td>
<td>Pain Ngl.</td>
<td>10.0</td>
</tr>
<tr>
<td>IX</td>
<td>Pain Ngl.</td>
<td>11.4</td>
</tr>
<tr>
<td>X</td>
<td>Pain Ngl.</td>
<td>15.9</td>
</tr>
</tbody>
</table>

improvement started rather suddenly after a 15-week period of placebo tablets. In case no. VIII the curve started falling after approximately 10 weeks of Dicumarol treatment, declined for another 10 weeks, and remained more or less stationary during the ensuing periods.

The 6 nitroglycerin consumption curves for long intervals ran remarkably parallel to the pain report curves, following closely even minor variations. The decline of the pain report curves of cases nos. VI and VIII was equally marked in the corresponding nitroglycerin consumption curves. A rather marked fall in nitroglycerin consumption also took place during the first Dicumarol periods

TABLE 3.—Statistical Analysis of Average Values for Pain and Nitroglycerin Consumption

<table>
<thead>
<tr>
<th></th>
<th>Degrees of freedom</th>
<th>Mean square</th>
<th>Variance ratio (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicumarol/placebo</td>
<td>1</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>130</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicumarol/placebo</td>
<td>1</td>
<td>240.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>80.7</td>
<td></td>
</tr>
</tbody>
</table>

Conditions during the last 4 weeks of all the Dicumarol periods (case I IH excepted) and all the placebo periods are compared by variance analysis. No difference is found on the 5 per cent significance level.

of cases nos. IV and VII. However, in the preceding placebo period of case no. IV the consumption was lower than during any time of the Dicumarol period in question, an isolated high peak during the first part of the Dicumarol period being a more conspicuous feature than the ensuing decline. In case no. VII the fall in nitroglycerin consumption started after approximately 22 weeks of Dicumarol treatment. Both in this case and in case no. VIII it might look as if the nitroglycerin consumption curves indicated a therapeutic effect of the drug. Since the nitroglycerin consumption curve of case no. VI showed a decline as pronounced as the pain report curve during the first placebo period, and a steady and marked fall occurred during placebo treatment from the forty-fourth to the seventy-sixth week in case no. X, it is evident that an explanation along these lines is scarcely tenable.

Table 2 gives the weekly averages for pain and nitroglycerin consumption during the first 4 weeks and the last 4 weeks of all Dicumarol and placebo periods for each individual.

These composite figures from the beginning and the end of the periods of each type of treatment might disclose any systematic tendency better than do the curves. The pain values are, however, much the same in all
columns, while a tendency toward reduction in nitroglycerin consumption during both Dicumarol periods and placebo periods is evident. A comparison between the nitroglycerin consumption during the last 4 weeks of each type of treatment discloses in 5 out of 6 cases, however, a higher average nitroglycerin consumption during the end of the Dicumarol periods than during the end of the placebo periods.

The results have also been evaluated by statistical methods. A comparison of the pain report values and the nitroglycerin consumption values for the last 4 weeks of each type of treatment discloses no significant difference between the therapeutic effect of the Dicumarol tablets and the placebo tablets (table 3).

**Discussion**

Keeping in mind the numerous errors that have been made in all fields of therapy while trying to evaluate new types of treatment, and considering the special difficulties encountered when the therapeutic efficacy on a purely subjective phenomenon like pain is to be judged, we think that the greatest caution should be exerted in formulating any conclusions. We feel justified in stating only that in this material, with the doses and courses of Dicumarol here administered, and with the methods of registration here employed, no specific beneficial effect could be traced from the use of Dicumarol in the treatment of the anginal pain.

**Summary**

An attempt was made to register by use of “report cards” the daily amount of pain and the weekly consumption of nitroglycerin tablets in 10 cases of angina pectoris during treatment by alternating courses of Dicumarol tablets and placebo tablets. Four subjects had previously suffered from myocardial infarction. All had had their symptoms for at least 1 year, and in 4 cases for more than 3 years. One died shortly after the initiation of the study, and only 6 managed to keep count of their nitroglycerin consumption. The total number of Dicumarol periods was 24, half of them lasting more than 6 months, during a total period of observation lasting for more than 2 years.

The results do not indicate that Dicumarol treatment has a greater effect than a placebo treatment on the cardiac pain in cases of angina pectoris of more than 1 year’s duration.

**Summary in Interlingua**

Esseva tentate registrar per medio de “cartas de reporto” le grados diurne de dolor e le consumption septimanal de tabletas de nitroglycerina in 10 casos de angina de pectore durante cursos alternante de therapia per tabletas de Dicumarol e per tabletas de medication fictitie. Quatro del subjectos havéa previemente suffrite de infarccimento myocardial. Omnes hava hibia lor symptomas durante al minus 1 anno, 4 durante plus que 3 annos. Un del subjectos moriva brevemente post le initiation del studio, e solmente 6 succedeva a manten le reportos de lor consumption de nitroglycerina. Le numero total del periodos de administration de Dicumarol esseva 24. Un mediate del illos durava plus que 6 menses. Le periodo total del observaciones esseva plus que 1 anno.

Le resultatos non indica que Dicumarol exercéa un plus forte effecto que le medication fictitie super le dolores cardiac in casos de angina de pectore de un duration de plus que 1 anno.

**References**

5. Lopes, E. C., and Molenaar, M. G.: Prolonged Dicumarol (bishydroxycoumarin) therapy in severe angina pectoris and in
TREATMENT OF ANGINA PECTORIS WITH DICUMAROL

Each case has its lesson—a lesson that may be, but is not always, learnt, for clinical wisdom is not the equivalent of experience. A man who may have seen 500 cases of pneumonia may not have the understanding of the disease which comes with an intelligent study of a score of cases, so different are knowledge and wisdom, which as the poet truly says, 'far from being one, have oft-times no connexion.'—Aequanimitas and Other Addresses. Blakiston & Co., Philadelphia, and T. K. Lewis, London, 1904.
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