Anticoagulant Therapy with Dicumarol Maintained during Major Surgery

By Sten Müllertz, M.B., and Ole Storm, M.B.

Most postoperative thromboses are probably initiated before or during surgical interventions and most of the fatal embolisms occur during the early postoperative period. As a complete prophylaxis, Dicumarol therapy was begun before, and maintained at an effective level during and after, major surgical interventions in 11 patients with a marked thromboembolic predisposition. No excessive hemorrhage, thromboembolic incidents or other unusual complications were encountered. The precautions necessary for a safe performance of the procedure are described.

Anticoagulant therapy with Dicumarol has been shown to reduce the incidence of thrombosis and embolism and has been used prophylactically after surgical interventions.1 In these cases the Dicumarol treatment was started during the first two postoperative days and became effective only some days later. However a large proportion of the fatal, postoperative pulmonary embolisms occur in this early period; and it is probable, that most postoperative thromboses are initiated before or during surgery. Therefore prophylaxis with Dicumarol against thromboembolic complications in surgery can be complete only when instituted before, and maintained during and after surgery. In some papers the results of Dicumarol treatment after surgical operations,4-8 after delivery,7-8 during emergency operations,9,10 in experimental surgery,11 and during some forms of vascular surgery12 have suggested that no risk of uncontrollable hemorrhage should be expected in a properly administered Dicumarol therapy during surgery. In a small group of surgical patients with a strong thromboembolic predisposition and a bad general physical condition, the risk of hemorrhage by continuous treatment with Dicumarol was preferred to the risk of thromboembolism.

It is the aim of the present paper to demonstrate that a Dicumarol treatment can be maintained before, during, and after major surgery without increased hemorrhage or other complications when the treatment is carefully controlled by a reliable and sensitive method.

Method

Dicumarol produces a decrease in the level of proconvertin (factor VII) and prothrombin in blood.12 The effect of the treatment was followed by a one-stage assay of the combined effect of proconvertin and prothrombin13 as described by Astrup, Müllertz and Rud Hansen.14 A saline buffer extract of human brain, stored at −20 C. was used as thromboplastin. Oxalated ox plasma, freed from prothrombin and proconvertin by adsorption and stored at −20 C., supplied proaccelerin (factor V) and fibrinogen. Plasma from oxalated human blood (9 volumes blood + 1 volume potassium oxalate, 2 per cent) was diluted 1:10 with a buffer-oxalate-saline mixture. In test tubes 0.2 ml diluted plasma, 0.2 ml thromboplastin, and 0.2 ml adsorbed ox plasma were mixed and recalified at 37 C. with 0.2 ml of a calcium chloride solution (optimal concentration, approximately 30 mM). The clotting times were converted into percentages of normal by interpolation on a correlation graph prepared from dilutions of a mixture of several normal plasma samples. The advantages and accuracy of this method have been studied.15 The usual prothrombin tests, in which a dried thromboplastin reagent and undiluted plasma are used, are less reliable,14,15 and were not considered safe enough for our purpose.

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Procedure

A reduction of the thromboembolic morbidity is generally obtained when the proconvertin-prothrombin level is kept below 30 per cent of the normal value. Below 5 per cent, there is an increased risk of major hemorrhage, above 10 per cent the risk is small. It was planned to induce an initial fall in proconvertin-prothrombin to a level of 10 to 20 per cent. A level between 20 and 30 per cent on the day of operation was considered desirable. Generally the treatment was begun four to six days before operation to allow time for the determination of the approximate maintenance dose of Dicumarol. After operation the level was maintained between 10 and 30 per cent until the patient was effectively ambulatory (two to four weeks). Dicumarol tablets of 20 mg. were used to allow changes in dose of 10 mg. (= one half tablet). Accidental low levels could be corrected to therapeutic and safe levels by oral administration of 50 mg. of menadione sodium bisulphite. In case of severe hemorrhage a safe level could be reached quickly by transfusions of fresh blood and by intravenous administration of 250 to 500 mg. of vitamin K₁ in a water emulsion.

In the dosage of Dicumarol attention was given the delayed response (one to two days), the protracted cumulative effect (about two days for small doses, five to seven days for large doses), and the large individual variations in tolerance. As it is difficult to foretell the response of any patient to Dicumarol, 300 to 400 mg. Dicumarol were given during the first two days, and the subsequent dosage

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**Fig. 1.** The dosage of Dicumarol and the proconvertin-prothrombin level in blood before, during, and after surgical interventions in 11 cases (see case reports). The daily doses of Dicumarol (in milligrams) are shown in the upper parts, the proconvertin-prothrombin-levels (in per cent of the normal level) in lower parts of the chart. The horizontal lines at 10 and 30 per cent indicate the therapeutic range for an effective antithrombotic prophylaxis without risk of hemorrhage. The time of operation is indicated with arrows. The proconvertin-prothrombin level was determined immediately before, during, and one to three hours after the operation, in cases 6, 10, and 11 only, before and after the operation.
was determined by the response to the first doses, and to the expected postoperative decrease in the proconvertin-prothrombin level. (See below.)

The transient rise in the level during the operation (fig. 1), was caused by the proconvertin and prothrombin of the transfused blood. This had no apparent effect on the level of the next day and was left out of consideration in the planning of the dosage.

Observations

The Postoperative Decrease in Proconvertin-Prothrombin Level

The proconvertin-prothrombin levels of the 11 patients treated with Dicumarol in the days before, during, and after the surgical intervention (indicated by arrows) are shown in figure 1. During our investigation it became obvious that the proconvertin-prothrombin level decreased markedly in the early postoperative period. This was especially pronounced in cases 5 and 7, in which Dicumarol doses of the same magnitude were followed by increasing levels before, and decreasing levels after the operation. The decrease did not occur in cases 10 and 11. In most cases the Dicumarol doses were reduced or withheld in the postoperative period (cases 2, 3, 4, 6, 8, 9) and in two cases menadione (50 mg doses) was administered orally with immediate but variable effects (cases 9 and 6).

The proconvertin-prothrombin level was followed in a number of patients undergoing similar surgical interventions without Dicumarol treatment. A definite postoperative decrease was observed in three patients (fig. 2, cases 1, 3, 4), a small decrease in two patients (fig. 2, cases 2 and 5), while no significant change was observed in case 6. These results are in accordance with those of Warren and Belko.20

The postoperative decrease may be caused by an increased consumption and/or a decreased production of these factors and may be associated with a lowered tolerance to Dicumarol.

The individual variations of the postoperative decrease make the dosage difficult during and after the operation. The establishment of a level between 20 and 30 per cent during the operation and a reduction of the Dicumarol doses on the day before and on the day of operation are now considered to be important precautions against dangerously low postoperative levels.

Clinical Results

Dicumarol treatment was administered to 11 patients who were predisposed to postoperative thromboembolism. The predisposition was caused by different factors known to produce a high incidence of thromboembolism:2 nine of our patients had had previous thromboembolic episodes and five had degenerative heart disease (two with previous coronary occlusion). Three of our patients had marked generalized arteriosclerosis, five had cancer of the lung and seven had chronic infections. One was obese, four were 60 years of age or older and six were in very bad physical condition. In nine patients extensive
surgical operations made the postoperative mobilization less effective. In six patients surgery of the lung exposed the patient to an increased release of thromboplastin into the blood.

The following surgical interventions were performed during Dicumarol therapy: Pneumonectomy in four patients; exploratory thoracotomy in one patient; thoracoplasty in two patients; extrapleural pneumonolysis in one patient; decortication of the lung in one patient; uterine curettage (therapeutic abortion) in one patient; exploratory laparotomy (large incision for gastrectomy) in one patient.

The dosage of Dicumarol and the proconvertin-prothrombin level in the days before, during and after operation are shown in figure 1. During the operation it was about 30 per cent in six patients (cases 2, 4, 5, 6, 7, 10), between 20 and 30 per cent in two patients (cases 3, 8) and between 10 and 20 per cent in three patients (cases 1, 9, 11). The amount of hemorrhage during the operation was evaluated by two experienced surgeons. In thoracic surgery large vessels and large muscles are transected and especially in thoracoplasty, extrapleural pneumonolysis, and decortication of the lung hemostasis cannot be complete. Any abnormal bleeding should be easily discovered in thoracic surgery and in uterine curettage. The postoperative hemorrhage in thoracic surgery was evaluated from the volume of the fluid collected by drainage and aspiration from the thoracic and extrapleural cavities. The normal postoperative hemorrhage and the normal amount of blood transfused in a series of similar operations are shown in table 1.

Case Reports

The amount of blood transfused during operation and the hemorrhage during and after operation were normal or below normal average, when not expressly otherwise stated. The postoperative courses were uneventful except in cases 4 and 8. No deaths occurred.

Case 1. This male patient, 55 years of age, had cancer of the lung, hypertension, arteriosclerosis, coronary sclerosis and a history of a previous attack of coronary occlusion. During pneumonectomy 1500 ml. blood were transfused and the blood loss was 700 ml. (estimated by weighing). The postoperative hemorrhage was 1210 ml. The patient was treated with Dicumarol for nine days before and 24 days after operation.

Case 2. This patient, a man 62 years of age, had cancer of the lung, arteriosclerosis, myocardial degeneration and a previous attack of coronary occlusion. During pneumonectomy 1500 ml. blood were transfused. The postoperative hemorrhage was 680 ml. The patient was treated with Dicumarol for four days before and 34 days after operation.

Case 3. This man, 57 years of age, with cancer of the lung and previous attacks of thrombophlebitis, also suffered from extensive varicose veins of both legs. Dicumarol treatment was initiated, and high ligation of the saphenous veins was performed. Pneumonectomy was performed seven days later during Dicumarol therapy. During operation profuse bleeding (approximately 800 to 1000 ml.) occurred through a tear in the pulmonary artery. The total blood loss during the operation was 1500 ml. (estimated by weighing); 2000 ml. blood were transfused during operation and 1000 ml. blood after the operation (normal 2500 ml., table 1). Apart from this, no abnormal bleeding was observed. The postoperative hemorrhage was 1570 ml. The patient was treated with Dicumarol for eight days before and 11 days after operation.

Case 4. This patient, a woman 59 years of age, had cancer of the lung, syphilis, angina pectoris and degenerative heart disease. During pneumonectomy 1500 ml. blood were transfused; five hours after operation the patient went into shock and 2000 ml. blood were transfused (normal 2500 ml., table 1). At this time the proconvertin-prothrombin level had increased above 37 per cent and the hemorrhage was

<table>
<thead>
<tr>
<th>Operation</th>
<th>No. of Cases</th>
<th>Transfused Blood (ml.)</th>
<th>Postoperative Hemorrhage (ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>5 Cases below</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>50</td>
<td>2500</td>
<td>1520</td>
</tr>
<tr>
<td>Exploratory Thoracotomy</td>
<td>50</td>
<td>1000</td>
<td>570</td>
</tr>
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<td>Extrapleural Pneumonolysis</td>
<td>50</td>
<td>1000</td>
<td>700</td>
</tr>
<tr>
<td>Thoracoplasty</td>
<td>50</td>
<td>1000</td>
<td>560</td>
</tr>
</tbody>
</table>

Transfused blood: The amount transfused during the operation and the first 24 hours. The postoperative hemorrhage was determined from the amount of blood collected by drainage and aspiration.
not abnormal. The total amount of hemorrhage through the pleural drain was normal (1300 ml.). The patient was treated with dicumarol for three days before and 11 days after operation.

Case 5. This man 67 years of age, suffered from empyema, hypertension, arteriosclerosis, and pericarditis. A large thrombophlebitis of the left leg was treated with Dicumarol. The symptoms disappeared, and 18 days after initiation of treatment decortication of the lung was performed. During the operation 1000 ml. blood were transfused. The postoperative hemorrhage was 490 ml. Later a purulent secretion was discharged through the drain. The hemorrhage was not unusual as compared with 7 similar operations. The hemorrhage in these patients was difficult to evaluate because of the empyema. The patient was treated with Dicumarol for 17 days before and 19 days after operation.

Case 6. This female patient, 38 years of age, had tuberculosis of the lungs. A left extrapleural pneumonolysis was performed without Dicumarol treatment and a thrombosis of the left axillary and brachial vein occurred seven days after the operation. Dicumarol was immediately administered with good effect and maintained during thoracoplasty on the right side 12 days later. During this second operation 1000 ml. blood were transfused. The postoperative hemorrhage was 200 ml. The patient was treated with Dicumarol for 12 days before and 14 days after the second operation.

Case 7. This man, 61 years of age, had pulmonary tuberculosis. A pleuropneumonectomy was performed for a destroyed left lung. At the operation a total thrombosis of the left pulmonary artery was found, and Dicumarol was immediately administered. Thoracoplasty was performed during this therapy 11 days later. During the second operation 500 ml. blood were transfused. The amount of fluid from the pleural drain after thoracoplasty (1800 ml.) was above normal but the amount of hemorrhage due to the last operation was difficult to evaluate because of the preceding pleuropneumonectomy and a complicating empyema. The patient was treated with Dicumarol for 10 days before and 16 days after operation.

Case 8. This patient, a man 58 years of age, suffered from tuberculosis and thrombophlebitis of the left arm. During extrapleural pneumonolysis 1500 ml. blood were transfused (normal 1000 ml.), but the bleeding did not appear to be more than normal. His postoperative condition was very bad, there being intense cyanosis and dyspnea and latent shock. A markedly decreased tolerance to Dicumarol entailed a low proconvertin-prothrombin level postoperatively (5 per cent) and the postoperative hemorrhage was 1400 ml. (normal 700). On the seventh postoperative day 1000 ml. blood were transfused. His condition promptly improved and the course of recovery was uneventful. The patient was treated with Dicumarol for three days before and nine days after operation.

Case 9. This female patient, 58 years of age, had sarcoidosis of the lungs, degenerative heart disease, previous postoperative thrombophlebitis, and marked obesity. Exploratory laparotomy for a suspected carcinoma of the stomach was performed, but normal conditions were found. The blood loss was completely normal. The patient was treated with Dicumarol for 5 days before and 12 days after operation.

Case 10. This man, aged 65, suffered from cancer of the lung, arteriosclerosis, dilated aorta and myocardial degeneration. During exploratory thoracotomy 1000 ml. blood were transfused. The postoperative hemorrhage was 280 ml. The patient was treated with Dicumarol for six days before and 19 days after operation.

Case 11. This patient was a woman, aged 37, with pulmonary tuberculosis. She was also three months pregnant and gave a history of several previous prolonged episodes of thrombophlebitis. Uterine curettage (therapeutic abortion) was performed. The blood loss was normal during and after the operation and no transfusions were given. The patient was treated with Dicumarol for eight days before and 14 days after operation.

Summary. Surgical operations were performed on these patients at proconvertin-prothrombin levels varying from 12 to 36 per cent. During operation, blood loss was not excessive in any case, though hemorrhage was above normal in the patient whose pulmonary artery was accidentally torn. After operation hemorrhage was very small in two cases, normal in most cases and slightly above normal average in two cases. In one of these two patients the hemorrhage was difficult to evaluate because of a preceding pleuropneumonectomy and a complicating empyema; in the other the proconvertin-prothrombin level was rather low postoperatively. In no case did excessive hemorrhage occur.

Discussion

The prophylactic effect of Dicumarol and similar agents against thrombosis and embolism has been especially striking in cardiovascular diseases with a high incidence of thromboembolic complications.14,16,21 In Dicumarol therapy following surgery the evidence for a beneficial effect is less convincing.
In some series the incidence of thromboembolic episodes has been significantly reduced\textsuperscript{3, 22} but in other series with carefully composed control groups the reduction is relatively small.\textsuperscript{1, 5, 6, 23} The reason may be (1) that the treatment has been partly ineffective because of lack of reliable methods of control or (2) that the treatment has become effective too late after the operation.

In surgery a vast number of vessels are injured and large amounts of tissue thromboplastin enter the blood stream. At the same time local and general circulatory disturbances are inevitable. The peak of incidence of fatal pulmonary embolisms was found by Eyo\textsuperscript{2} to occur on the seventh day after operation; 25 per cent of the total number of deaths had occurred by the fourth day, and 60 per cent by the seventh day after operation. Consequently postoperative thromboses are probably initiated before and during the surgical intervention. Allen\textsuperscript{3} found that early thromboses should be treated by anticoagulant therapy within 24 hours to avoid embolism. Generally, postoperative anticoagulant treatment has been instituted on the first, second, or third day after operation; and relatively small initial doses have been used. Consequently the prothrombin-proconvertin concentration may not reach an effective level until four to seven days after operation. Administration of large doses of Dicumarol (or related compounds) after operations in order to obtain an early effective anticoagulant effect will produce unpredictable and often dangerous responses because of the postoperative decreased tolerance to Dicumarol.

It may be concluded, therefore, that an effective and controlled prophylaxis against thromboembolism in surgery can be obtained with Dicumarol only when the treatment is begun prior to and maintained during and after the operation. Obviously, uncontrollable hemorrhage is the main risk of this procedure. The spontaneously occurring hemorrhage during Dicumarol therapy has generally been slight, but not infrequently serious, and in a number of cases fatal bleeding has developed.\textsuperscript{24} It is probable, however, that most instances of major hemorrhage have been caused by excessive doses of Dicumarol administered with inadequate methods of control.\textsuperscript{1} This view is strongly supported by the very few instances of slight hemorrhage in long-term treatment which is carefully controlled by reliable methods.\textsuperscript{16, 23}

The incidence of hemorrhage in patients treated with Dicumarol after surgery\textsuperscript{2, 4, 5} and after delivery\textsuperscript{7} was not larger than in other groups of patients, and excess bleeding from the wounds was not noted. Uterine curettage, caesarian section, manual release of placenta,\textsuperscript{8} vein transplantation (two cases), and transfixation of arteriovenous fistulas (two cases)\textsuperscript{12} have been performed without abnormal bleeding in patients previously dicumarolized. However, in the patients just referred to the prothrombin times during operation were not stated. In two known instances an emergency appendectomy has been performed without complications during Dicumarol therapy on patients with prolonged prothrombin times.\textsuperscript{9, 10} In experimental surgery on dogs,\textsuperscript{11} complete hemostasis in open wounds of the spleen could be obtained at prothrombin levels above and somewhat below 10 per cent of the normal, while the hemorrhage was uncontrollable at lower levels. Consequently, uninterrupted Dicumarol treatment during surgery necessitates the use of a standardized, accurate, and sensitive method for the control of the therapy, meticulous care in the dosage of Dicumarol, and a close clinical control of the patients. The moderate coagulation defects which occur under these conditions can be corrected in a very short time by blood transfusions and intravenous administration of vitamin K\textsubscript{1}.\textsuperscript{18, 19}

All of our group of patients showed a strong predisposition to thromboembolic incidents. Six patients had cancer of the lung. In a large series of patients of this category 30 per cent died in the postoperative period, 18 per cent of these deaths were caused by pulmonary embolism, and 12 per cent by coronary occlusions.\textsuperscript{26} We consider a thromboembolic risk of this magnitude to be considerably
greater than the risk of hemorrhage in properly administrated Dicumarol therapy maintained during surgery.

Summary

1. Anticoagulant therapy with Dicumarol was instituted before and maintained at an effective level during and after major surgical interventions in 11 patients with a marked predisposition to thromboembolism. No excessive hemorrhage and no unusual complications were encountered.

2. A marked transient decrease in the level of proconvertin-prothrombin in blood occurred generally after large operations.

3. A standardized and sensitive method for the control of the therapy, and experience and care in regulating the dosage of Dicumarol are indispensable for a safe performance of the procedure.

4. In this way an effective prophylaxis against postoperative thromboembolic complications can be provided.

Sumario Español

1. Terapia anticoagulante con Dicumarol se instituyó antes y se mantuvo a un nivel efectivo durante y después de intervenciones quirúrgicas mayores en 11 pacientes con marcada predisposición a tromboembolismo. No se encontraron hemorragias excesivas o complicaciones fuera de lo usual.

2. Un marcado transitorio decremento en el nivel de proconvertin-protrombina en la sangre ocurrió generalmente luego de operaciones mayores.

3. Un método regularizado y sensible para el control de la terapia y experiencia y cuidado en la regulación de la dosificación del Dicumarol son indispensables para poder ejecutar este procedimiento inocuamente.

4. De esta manera se puede proveer una profilaxis efectiva para las complicaciones tromboembólicas post-operatorias.

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