1950

Dicumarol in coronary thrombosis

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SENIOR THESIS

DICUMAROL

IN

CORONARY

THROMBOSIS

by

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PRESENTED TO THE COLLEGE OF MEDICINE

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OMAHA 1950

INTRODUCTION

The purpose of this paper is to determine the relative usefullness of (3.3'Methylenebis) (4-Hydroxycoumarin) or dicumarol in the prevention and treatment of coronary thrombosis. An attempt is made to report the latest information found in the literature on experimental studies, indications and contraindications of dicumarol in coronary thrombosis, action of the drug and its present and expected theraputic value.

HISTORY AND DEVELOPMENT OF DICUMAROL

Independent studies by Schofield in Canada and Roderick in the United States demonstrated that a hemorrhagic diathesis resulted in cattle eating improperly cured common sweet clover, hay, or silage. It was later shown by Roderick and confirmed by Link and co-workers and by Quick that the faulty coagulation mechanism was due to insufficient prothrombin.

In 1941 Link and his associates at the University of Wisconsin reported the isolation of 3.3'-methylenebis (4-hydroxycoumarin) from spoiled sweet clover, identified it as the factor responsible for the hemorrhagic diathesis in cattle, and synthesized the compound.(24)

Shortly following this, two groups, headed by Meyer at the University of Wisconsin and by Butt, Allen and Bollman at the Mayo Clinic, began clinical studies on "Dicumarol" as a means of retarding intravascular clotting in human beings. They and others have shown that "Dicumarol", carefully administered, with daily determination of the prothrombin time, is of value in the prophylaxis and treatment of intravascular clotting.

EFFECTS OF DICUMAROL IN PREVENTION OF THROMBOSIS

Since the identification and synthesis of Dicumarol several questions have to be answered concerning it:[4]

1. Does the lowering of prothrombin content of blood prevent or delay experimental thrombosis?

In answer to this question, Martin, Laufman and Lantern[1] by their latest experiment using Knisely's technique, were able to produce sludge at will and observe results. The sludge masses of blood cells may serve as a matrix for thrombus formation provided other conditions favorable to thrombosis are present.

When anticoagulants are administrated, thromboses do not generally occur in small vessels distal to an occlusion, but such doses do not prevent formation of sludge. Administration of anticoagulants prevents thrombus formation in the presence of sludge by preventing the slugged masses of cells from becoming adherant to the endothelial lining of the vessel. Sludge formation however is not prevented by giving dicumarol.

Dicumarol causes a reduction of the adhesiveness of the platelets suggesting a second factor by which the drug may produce an anti-clotting effect.[2]

2. Can the drug be given without producing untoward reactions? If so, can they be controlled?

It has been found that the erythrocyte sedimentation rate is frequently increased after the administration of

dicumarol, however, numerous tests including liver function studies, blood non-protein nitrogen, and sugar, erythrocyte and leukocyte counts, the fragility of erythrocyte, blood platelet's and urinary findings are not influenced. Dicumarol occasionally produces nausea, vomiting, and mild diarrhea, but the only serious toxic effect is bleeding which can be avoided except in minor degree by correct dosage based on serial prothrombin time determinations. If there is any evidence of bleeding, it can usually be controlled by giving 60 mgm. vitamin K intra-venously or by fresh whole blood transfusion.(3)

CONTRAINDICATIONS TO USE OF DICUMAROL

Absolute contraindications of use of dicumarol:

1. Sub acute bacterial endocarditis
2. Blood dyscrasias with tendency to bleeding
3. Renal insufficiency
4. Purpura of any type
5. Heart diseases with symptoms of decompensation, severe myocardial degeneration or blood pressure over 200.(5)

Relative contraindications:(6)

1. Pregnancy and first 3-5 days of the puerperium.
2. Existence of ulcerative leisons, open wounds and potentially bleeding surfaces.
3. Necessity for second surgical operation during first two weeks post operative.
4. Vomiting due to gastric or intestinal obstruction.
5. Operations on brain and spinal cord.

MODERN TREATMENT OF CORONARY THROMBOSIS

The most important forms of treatment in acute myocardial infarction are relief of pain, rest and reassurance. For pain it is wise to give 1/4 - 1/2 grain doses of morphine sulfate hypodermically. If the pain is not relieved in thirty minutes 1/4 grain doses should be repeated at hourly intervals. Atropine sulfate 1/150 to 1/50 should be given with each hypodermic (according to Stroud et al).[7] If the patient is not relieved within a few hours 7 1/2 grains of aminophyllin may be given. Quinidine should also be used if indicated.

The patient should be allowed to assume as comfortable position as possible and, unless there are contra-indications, to turn from side to side at intervals.[7]

The patient should be reassured and the doctor should caution the relatives to show no apprehension when visiting him.[7]

He should be on a liquid diet high in carbohydrates and particularly during the febrile period. Small feedings of semi-solid and solid foods should be given later.[7]

If the patient is apprehensive he may be given ½ grain phenobarbital up to four times per day unless the blood pressure is too low. If there is any breathlessness or cyanosis, oxygen is indicated.[7]

In using dicumarol in conjunction with the previous treatment for coronary thrombosis it must be remembered that there is a lag of 48 hours in the effect of the drug,

but that thereafter the effect is cumulative. It therefore seems plausible that dicumarol therapy should be started immediately once it is recognized that the patient has had a recent coronary thrombosis.

Dicumarol is a tasteless odorless drug put up in 50-100milligram capsule sizes. A prothrombin determination should be done before administering dicumarol to the patient to find his normal blood level. Three hundred milligrams are then given. The following day another determination is made and unless the prothrombin time is markedly prolonged, therapy is continued on a maintenance dose of 100-200 mg daily. The normal time is approximately 17-20 seconds. One should attempt to maintain the patient between 34-40 seconds.(8)

OBJECTIVES IN USE OF DICUMAROL

The object of using dicumarol in acute coronary thrombosis is to reduce the mortality rate and decrease the severity of the acute episode through the following possible mechanisms:(9)

(1) Prevention of extension of the initial coronary thrombosis.
(2) Prevention of a second myocardial infarction during the healing stage.
(3) Prevention of formation of mural thrombi within the heart, thus avoiding all peripheral systemic emboli and some pulmonary emboli.
Prevention of thrombophlebitis developing in the legs and pelvis during convalescence thus avoiding the primary source of pulmonary emboli.

RESULTS OF DICUMAROL THERAPY IN CORONARY THROMBOSIS

Reports in the literature indicate that the usual theraputic proceedure is first to get a prothrombin determination, to then administer 300 mg dicumarol and then to maintain the patient on a dosage schedule of 50, 100, or even 200 mg. of dicumarol per day. The prothrombin time is followed by daily determinations and the patient's level kept in the neighborhood of 30-40 seconds.

Nichol et al [9] report a series of 44 patients treated with dicumarol after the diagnosis of coronary thrombosis was established. Standard anticoagulant treatment was given with a mortality rate of 16 per cent. All those with first attacks survived.

Peters et al [10] had a series of 110 cases of coronary thrombosis. Sixty patients received the accepted treatment and fifty received the usual treatment plus dicumarol. The incidence of clinical embolism was 16 per cent in the non-dicumarolized group and 2 per cent in the dicumarolized group. The mortality rate in the former group was 20 per cent and in the latter was 4 per cent.

A series of 46 cases of acute coronary thrombosis treated with dicumarol is reported by Wright.[11] Forty one of the 46 patients ceased having embolic episodes as soon as the prothrombin time was brought down to theraputic levels. Only 24 per cent of the 46 died as contrasted with the usual mortality of 60 per cent.

Nichol et al [12] report a series of 64 patients treated with dicumarol during 70 attacks. Forty of these episodes were first attacks. Mortality in this group was only 2.5 per cent or 1 death, whereas in the remaining patients with second, third, etc., attacks it was much higher i.e. 15.7 per cent or 11 deaths.

Five patients in this series [12] had had multiple attacks of coronary thrombosis. They were given dicumarol for from 6-32 months in an attempt to forestall additional acute episodes. One patient was free of attacks for 3 years, the last 21 months of which he was on dicumarol, but he developed a fourth attack which proved fatal. However the author did not believe he was properly dicumarolized. Another patient had had 3 attacks in 13 months but has now gone 3 years without attacks while taking dicumarol.

Parker [13] reports a series of 50 cases with a 10 per cent mortality rate in the dioumarolized, and a 13 per cent mortality in the nondicumarolized patients.

McCall [14] in a group of 71 patients treated with dicumarol, had 9 deaths or a 12.5 per cent mortality. These were the result of heart failure, ruptured ventricles, pulmonary infarction or extension of the myocardial infarction. His conclusion is that this type of therapy is justified by the resultant low incidence of thromboembolic phenomena, which insures a less stormy convalescence.

Hilton et al [15] report a large series of 800 cases using a control group and standard dicumarol therapy. They

found a mortality of 23 per cent in the control group as contrasted with a 13 per cent in the dicumarolized cases.

The latter result i.e. 13 per cent [15] tallies closely with the 16 per cent mortality noted by Reich et al [16] in their group of 35 dicumarolized cases.

Of the 240 patients with acute myocardial infarction in which dicumarol was not used. Billings et al[17] found a mortality of 40.4 per cent within 30 days of the acute episode. This rose to 53.6 per cent with second and third attacks.

RECENT EXPERIMENTS WITH DICUMAROL

Kashdan et al[21] working with rabbits, produced clotting in the jugular veins. Nine to 14 days later heparin and dicumarol were given and prothrombin times were kept above normal limits for the next two weeks. Both caused resumption of clinical patency in a number of veins which had been occluded for 4 days or longer.

Macht[22] in experiments on animals, found that injections of penicillin exert thromboplastic effects. The coagulation time was also shortened by streptomycin. It was also found that hemorrhagic tendencies could be controlled by penicillin injections. Therefore, when administering antibiotics one should be on guard for thromboembolic phenomena and, where massive doses are used, dicumarol should be administered.

Reich et al[8] report that dicumarol can be synthesized from salicylates and that while the latter are only one-twentieth as active in anticoagulant activity, the combined effect may cause an intensely prolonged prothrombin time. Thus salicylates should probably not be given to the patient while he is on dicumarol therapy.

Moloney et al[20] carried out experiments on 11 patients using 700-900 miligrams of dicumarol over a 7 day period. They found that there was a greatly prolonged clotting time of whole blood in determination with drifilm tubes. Glass tubes did not accurately reflect this coagulation defect.

The data presented in this experiment[20] tend to support the clinical impression that intravascular clotting may be prevented, at least in part by amounts of dicumarol which fail to depress the prothrombin activity of the blood to levels hitherto considered necessary for the inhibition of clotting.

CONCLUSIONS

The use of anticoagulants has decreased the incidence of mural thrombi and other thrombo-embolic phenomena markedly and has been accompanied by a significant decrease in the mortality rate. Decreases in mortality are not as pronounced as the diminished incidence of thrombo-embolism because there are many other mechanisms of death in these cases. The

initial shock due to acute myocardial failure may be fatal as may progressive myocardial decompensation and cardiac rupture. Many cases die suddenly with no cause demonstrable even at autopsy. It is believed that the most common cause in this group is cardiac arrhythmia, especially ventricular fibrillation. In coronary thrombosis good nursing care is essential and well established treatment such as oxygen, papaverine, quinidine and sedation should be given when indicated. These measures should not be forgotten in the enthusiasm for anticoagulant therapy.(3)

It must be remembered that 3 days or longer are necessary to obtain a theraputic prothrombin level but it also takes an interval of 5 days after infarction before mural thrombi form, so there is time for prothrombin depletion.(23) It is emphasized that the main usefullness of anticoagulant therapy in coronary disease in the prevention of embolization either from peripheral veins or from cardiac mural thrombi.

There seems to be an increased clotting tendency in most of the cases of acute coronary thrombosis. This is manifested by a decrease in the clotting time of diluted plasma.(10)

Many authors believe that digitalization for congestive failure in coronary thrombosis increases the incidence of thromboembolic complication. This hazard, if true, may be diminished by the dicumarolization of such patients.

The incidence of embolism as a complication of coronary thrombosis has been significantly reduced by keeping prothrombin activity between 30-40 per cent of normal during active treatment and early convalescence - a period of six weeks.

After dicumarol has been discontinued and prothrombin has returned to normal, the risk of further coronary attacks is the same as before. However it must be remembered that Nichol et al[12] have kept patients free of attacks for from 13-32 months using dicumarol prophylaxis. Hence the risk of subsequent attacks may be diminished by prophylactic anticoagulant therapy.

Experiments of Moloney et al[20] with the drifilm technique may prove of importance in the prophylactic treatment of coronary thrombosis. Further study must be done before proper evaluation may be made.

The number of thromboembolic phenomena and fatalities complicating myocardial infarction are sharply reduced by anticoagulant therapy when carried out under hospital management with careful assay of prothrombin times during the course of treatment. Any patient who shows a thromboembolic episode after a recent myocardial infarction deserves to be placed upon dicumarol therapy.[18]

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