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Long-term postinfarctional anticoagulation

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FORWARD

By Dr. Gordon Myers of Boston Mass.

Thumbnail Sketch of Man Least Likely to Have Coronary Heart Disease

An effeminate municipal worker or embalmer,
completely lacking in physical and mental
alertness and without drive, ambition or competetive
spirit, who has never attempted to
meet a deadline of any kind.
A man with poor appetite, subsisting on fruits
and vegetables laced with corn and whale oil
Detesting tobacco,
Spurning ownership of radio, TV, or motor car
With full head of hair and
Scrawny and unathletic in appearance;
Yet constantly straining his puny muscles
by exercise.
Low in income, blood pressure, blood sugar,
uric acid and cholesterol,
Who has been taking nicotinic acid,
pyridoxine and long term
anticoagulant therapy
Ever since his prophylactic castration.

LONG-TERM POSTINFARCTIONAL ANTICOAGULATION

Thus far, physicians have been striving to prevent infarctions and to prolong life after an infarction, but little, if any, progress has been made in the correction of the underlying pathologic process. Link suggested that a substance in spoiled, sweet, clover, hay which produced bleeding in cattle and labratory animals might be investigated for clinical usefullness.(19) Since that time, many papers have been published on the subject with widely varying conclusions. Due to the magnitude of the field of anticoagulation, this paper will be limited mainly to long-term treatment.

Mechanism of Clotting

Although myocardial infarction is due only secondarily to intravascular clotting, let us consider the mechanism of clotting before discussing anticoagulants. Blood will not clot within an anatomically and physicologically normal vessel. The normal vessel wall is negatively charged, due to a layer of heparin-like material, and repels the formed elements of the blood. The plasma proteins are also repelled by the negative charge. If a local lesion is present in the vessel wall the negative charge is broken by the presence of a cephalin-like material to which negatively charged particles in the blood (protein, platlets, etc.)

are selectively adsorbed. Blood flow is laminated in the vessel with the platlets distributed around the periphery.

Schematically, one might explain clotting as shown below (35):

I. Prothrombin $\xrightarrow[\text{(slow reaction)}]{\text{calcium ions, thromboplastin}}$ Thrombin

II. Plasma ACG (inert) $\xrightarrow[\text{(small amount)}]{\text{thrombin}}$ Serum ACG (active)

The serum ACG then increases the rate of I.

III. Prothrombin $\xrightarrow[\text{serum ACG (rapid reaction)}]{\text{calcium ions, thromboplastin}}$ Thrombin

IV. Fibrinogen $\xrightarrow{\text{thrombin}}$ Fibrin

Thromboplastin is a lipoprotein which is present in the tissues, especially lung, brain, and placenta. It is also present either in the platlets or in the plasma with an inhibiter. It is felt that calcium ions have an effect upon the structure of fibrin (24, 27, 31, 32, 35).

Anticoagulant Agents

There are two basic groups of agents which are used in the treatment of mycoardial infarction, the heparin and the heparin-like drugs and the "prothrombin-openic" agents.

Heparin and Heparin-like Agents

Heparin is the only clinically valuable agent in this group.(33) Heparin is a mucopolysaccharide which has

been difficult to study structurally because it resists crystallization. Heparin does not alter the plasma concentration of the clotting factors, but its strong electronegative charge inhibits the action of several enzymes and perhaps increases the repulsion of negatively charged particles. It impairs the ability of platlets to agglutinate, interfers with the conversion of prothrombin to thrombin, interfers with the action of thromboplastin on thrombin and interfers with the conversion of fibrinogen to fibrin.

Opinion is divided as to whether constant or intermittant levels of anticoagulation should be maintained, although the results seem to be about the same. Continuous intravenous drip may be administered by adding 150-200 mgm. of heparin to 500-1000cc of I.V. fluid. The rate of administration is then adjusted by determining the clotting time at 3-4 hour intervals.

Intermittant intravenous injections may be used with the dosage varying from 40-60 mgm. every 4 hours to 100-150 mgm. every 6-8 hours. Intramuscular injections may lead to the formation of hematomas; therefore, subcutaneous injection is perfered. The most common dosage is 75 mgm. every six hours; however, larger doses may be given at longer intervals. One may follow the course of anticoagulation

with clotting times half way between the doses and just before each injection. Others use not clotting time determinations and seem to get along quite well.

Heparin is most valuable for rapid anticoagulation immediately following an infarction. Since it prolongs the prothrombin time, care must be exercised when changing to the oral anticoagulants in order to avoid discontinuing heparin too early (24, 33).

Paritol is similar to heparin chemically and in action. It is active 2-4 times as long as heparin; however, possible adverse reactions include vasomotor collapse, urticarin-like reactions, increased BUN with renal disease and sometimes late alopecia (35).

Prothrombinopenic Agents

Campbell isolated dicumarol in 1939 while working in Link's labratory (19). Many related agents have been developed. Only the more common drugs will be described below. These drugs depress Factor VII almost to zero immediately. In 24-48 hours, prothrombin is lowered to 15-30% of it normal level. Factor X (Stuart-Power Factor) is probably lowered and Factor IX (Christmas Factor, Plasma Thromboplastin Component) is reduced almost to zero (19, 21, 24, 27, 28).

Dicumarol-like Agents

Bishydroxycoumarin (Dicumarol) is the prototype of

this group. Dosage consists of 250-300 mgm. the first day, 100-200 mgm. the second day and 25-100 mgm. for maintenance. The drug is effective 24-96 hours after therapy is discontinued. Its shortcomings include inconstant absorption, delayed and variable onset of action, effectiveness only by the oral route and slow return of coagulation factors to normal levels. (24)

Ethyl bisoumacetate (Tromexan) has been used more widely in Europe then here. Theraputic levels of anticoagulation can be obtained in 24-36 hours with an initial dose of 1500-1800 mgm. Three hundred mgm. 2-3 times daily is required for maintenance. The effect of the drug is gone 24-36 hours after withdrawal. The action of this drug is more labile and less predictable than that of Dicumarol. (24, 35)

Warfarin (Coumadin) produces effective anticoagulation in 24-36 hours. It can be used orally, intramuscularly or intravenously. The dosage on the first day should be 60-75 mgm., 15-20 mgm. on the second day and 2.5-10 mgm. for maintenance. Coagulation changes are converted to normal 36-48 hours after withdrawal. (24)

Anticoagulant No. 63, 4-hydroxycoumarin, 2 mgm./kg. produces effective levels of anticoagulation is 24-48 hours. The drug is quite reliable. A patient can be maintained

on 2-3 doses per week, but it takes 4-14 days for prothrombin times to return to normal. Also Vitamin K has no antagonistic effect. (35)

Indandione Drugs

Phenylindandione: The initial dosage is 150-200 mgm. while 50-150 mgm. is required for maintenance. The onset of action is more rapid then with Dicumarol, but it is difficult to maintain the desired level of anticoagulation and some patients are completely refractory. Vitamin K has no effect in returning coagulation defects to normal (24, 35).

The above agents are used in long-term management of the patient as well as after the first days of treatment.

Control of the level of Anticoagulation Therapy

The most common method used for the control of oral anticoagulants is the quick one stage prothrombin test. This test is performed by adding tissue thromboplastin and calcium to oxalated fresh plasma. The quick one stage prothrombin test measures only prothrombin, and Factor VII, however, this is not a problem since prothrombin, Factor VII, Factor IX and Factor X are usually depressed in parallel. (21, 24, 28)

Confusion may arise in the reporting of prothrombin results. "Prothrombin Activity" refers to a comparison of the patients prothrombin time to a curve constructed from

the dilution of control plasma.

$$\text{"Prothrombin Index"} = \frac{\text{Prothrombin control}}{\text{Patients prothrombin time}} \times 100$$

The best method of reporting consists of the patient's prothrombin time in seconds and the control in seconds. (24, 33)

The thrombotest has been investigated in Europe, but at this time it does not appear to be ready for general usage. (21, 28)

During the acute phase of an infarction one should maintain the prothrombin time at 2½ to 3 times that of the control. Determinations should be obtained 2-3 times a week. After the patient is discharged from the hospital the prothrombin time should be maintained at about two times that of the control with determinations every 1-2 weeks. One must remember that while changing from heparin to oral agents, that heparin will prolong the prothrombin time.

The Lee-White method of determining clotting time on whole blood is the most common method of controlling heparin therapy. Determinations may be done just prior to each dose. A clotting time of 2-3 times normal is considered desirable.

Antagonists

Occasionally one may wish to counteract the effect of anticoagulants which have been administered. Protamine Sulfate specificaly neutralizes the effect of heparin. One seldom needs to actively neutralize heparin, for if the

drug is withdrawn the clotting time soon returns to normal. (24)

The prothrombin times (with oral anticoagulants) may be reduced with 50-150 mgm. Vitamin K. This will last 4-6 days. Fat soluble vitamin K causes an immediate appearance of Factor VII with a return of prothrombin levels in three days. Water soluble vitamin K immediately reduces the prothrombin time to a prophylactic level. Prothrombin is rapidly replaced, but there is no return of Factor VII for 24 hours. If one chooses to withdraw oral anticoagulants, Factor VII and IX return in 3-4 days and prothrombin in 14 days. (15, 24, 26)

Clinical Aspects

Effectiveness of Anticoagulation

There is a great deal of disagreement regarding the value of anticoagulation. Generally, the American investigators reported results more favorable to anticoagulation than did others. Keyes noted a death rate three times greater in the control group than in the treated patients. (16) Kuhn reported twice the mortality rate in control patients as compared to treated patients. (17) Manchester (20) and Thomas (32) reported similar results. Wright (34) reported a lower death rate from thromboembolic complications in treated patients. Griffeth (8) indicated favorable results

in poor risk patients under 70 years of age and in good risk patients over 70. Russek found improved results only in poor risk patients regardless of age. (30)

Others (9, 10, 11, 13, 18, 25, 29) report either no benifit, insignificant benefit, or some results contradictory to some of the statements above which claim reduced mortality for given groups.

It appears that patients who develop shock within 48 hours after an infarction, develop an arrhythmia, develop heart failure or have a history of dyspnea have a much poorer outlook than the patients without these factors. The death rate in diabetics does not seem to be altered by anticoagulants.

Contraindications and Complications

The incidence of bleeding is increased with anticoagulant therapy. Wright (32) feels that 7% of patients have hemorrhagic phenomena which are due to or are aggravated by anticoagulants. The most frequent forms of bleeding are hematuria, epistaxis, easy bruizing, melena, hematemesis, and hemptysis. The patient may test his urine for occult blood 2-3 times a week.

Anticoagulants are contraindicated in unreliable patients, pericarditis, dissecting aneurysm, cerebral hemorrhage, head injuries, retinal hemorrhage, SBE, malignant

hypertension, polyarteritis nodosa, untreated pernicious anemia, and untreated leukemia. Hempotysis following a pulmonary infarction is not a contraindication. (2, 12, 26, 33)

Therapy may be a matter of individual choice in patients with hepatic disease, renal disease, peptic ulcer and pending surgery if adequate control is available. (5, 12, 24, 26)

Several factors potentiate anticoagulants. Aspirin, oral antibiotics, quinine, and phenylbutazone are examples of such factors. (2, 28) Steriods may reduce the prothrombin time. (2, 35)

Gastrointestinal malignancy may produce bleeding with anticoagulants. Occult malignancy also increases the incidence of thromboembolic phenomena. (22, 35)

Hemorrhage with atheromatous plaques are found in 70% of males dying of myocardial infarction. (3) The exact relationship to anticoagulants or the seriousness of the finding is not known, but there seems to be some increased mortality in patients under treatment. Anticoagulation immediately after an infarction has been reported to lead to extension of the infarction in some cases.

Withdrawal

An increased incidence of recurrent infarctions has

been noted following rapid withdrawal of anticoagulant agents. (1, 6, 24) This is especially true following bleeding. (31) Since a hypercoagulable state has not been demonstrated, possible explanations include 1) more subtle coagulation changes, 2) extension of the underlying pathology. (6)

Withdrawal is recommended over at least a four week period with prothrombin controls. (6)

Summary

Many agents have been advocated for anticoagulant therapy. Basically all of the drugs fall into two groups, those resembling heparin and dicumarol. Heparin is used in obtaining rapid anticoagulation and it is quickly inactivated. The dicumarol like drugs are used for maintenance therapy. With long-term anticoagulation, treatment is considered to be adequate when the prothrombin time is twice that of the control.

Some of the early reports by prominent American cardiologists reported results favorable to anticoagulation. European investigators and recent reports in general have suggested little if any benefit with anticoagulation compared to control series or patients receiving placebos. One must remember also that there is no agreement among advocates of anticoagulation concerning the groups of

patients which might be more likely to receive benefit from anticoagulation therapy.

At this time it appears that anticoagulation therapy does not significantly alter the prognosis of the patient following a myocardial infarction.

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