

Anticoagulants In The Treatment Of Myocardial Infarction—A Review

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Though there is much difference of opinion as to whether anticoagulants should be used in all cases of myocardial infarction or only in carefully selected patients, there can no longer be any doubt as to their effectiveness in reducing the mortality rate. In a recent article Friedberg (1) states that "it is an impressive fact that in virtually every series of cases, small or large, there has been a consistent finding that the mortality and incidence of thrombo-embolic complications have been reduced when anticoagulants have been used". In table I is summarized the evidence of six different groups of workers showing that the mortality rate of those treated with anticoagulants was much reduced when compared with control groups in which anticoagulants were not used.

There are two main schools of thought with regard to the use of anticoagulants in myocardial infarction. There are those who state that they should be used in all cases and there are those who state that they should be used only in those cases that are termed "poor risks". The committee of the American Heart Association recommend the use of anticoagulants in coronary thrombosis but Russek and his associates (2) recommend that all cases be divided into two main groups, good risks and poor risks, and that only the poor risks be treated with anticoagulants. He states that any patient who shows

evidence of the following in the first 24 hours should be classified as a poor risk, previous myocardial infarction, intractable pain, extreme or persistent shock, enlargement of the liver or any other signs of congestive failure, gallop rhythm, auricular fibrillation, diabetic acidosis, obesity or previous thrombo-embolic complications. In a series of 1047 cases, divided into good risks and poor risks, he states that the mortality in the good risks was only 3.1% as compared with 60% in the poor risks, and concludes that in good risk deaths only one out of every hundred could have been prevented by anticoagulants if they were capable of stopping all thrombo-embolic phenomena. He, therefore, recommends that the decision as to whether to use anticoagulants be based on the initial appearance of the patient, as the risk of haemorrhagic complications in the good risk patients is not outweighed by the therapeutic effects. Many workers agree with Russek including Littman (3) and Furman and Ball and associates (4). Others, however, feel that the drugs should be used in all cases and Friedberg (1) states that as it is difficult often to tell if a patient is in the low risk group or not, that anticoagulants should be used in all cases. I. S. Wright (5) showed that in a series of 1031 cases the mortality rate in the mild or moderate cases was reduced from 12.9% in the control group to 7.2% in the treated

group, which contradicts the evidence of Russek. Wright concludes that one should not try to predict the future course of the patient but treat all cases. From their studies Rotter and Meyer (6) agree that anticoagulants should not be withheld until evidence of complications arise but that they should be used in all cases.

This controversy is far from settled and it remains for the future to decide whether the anticoagulants should be used in all cases of myocardial infarction or only in certain selected groups.

Recently other workers have recommended that anticoagulants only be used when the blood is shown to be hypercoagulable as indicated by the heparin tolerance test. Beaumont (7) and his associates have shown that there are three distinct phases of coagulability of the blood after an infarction. There is a period of hypercoagulability following the first 24 to 48 hours after the attack, then there is a period of spontaneous hypercoagulability lasting roughly 7 days but showing much variation. This is followed by a period of late hypercoagulability, variable in degree, and lasting for several weeks. On the basis of these observations these authors recommend that heparin be used immediately after an attack but should not be used from the second to the seventh day unless the heparin tolerance test shows evidence of hypercoagulability. After the eighth day anticoagulants should be used and continued until the late phase of hypercoagulability is over as shown by the heparin tolerance test. Ogura showed that acceleration of clotting occurred in 78% of cases

appearing on the third day and lasting 3 weeks. Peel (8) concluded from his studies that the heparin tolerance test be used to determine whether anticoagulants are indicated. However, this method of regulating anticoagulant therapy is not yet in general use.

A Consideration of various Anticoagulants.

It has been stated by J. A. Lewis (9) that "the ideal anticoagulant for use in patients with myocardial infarction is not at hand". While most authors agree to this, there are at least ten anticoagulants which have been used with varying degrees of success in the treatment of this condition. Following is a discussion of these various agents.

The anticoagulants have been divided into two main groups:

1. Those that are effective only when taken parenterally;
2. Those that are effective when given by mouth.

1. Parenteral anticoagulants:—
 (1) Heparin — Discovered by a medical student in 1916, heparin had established itself as a useful anticoagulant long before the oral anticoagulants came into use. Heparin acts as an anti-thrombin and anti-thromboplastin, and prevents platelet agglutination. It is rapidly destroyed by the body. Because of its mode of action, heparin is effective in increasing the clotting time almost at once and reaches its full therapeutic effect in 5 to 10 minutes. The duration of its activity is 4 to 5 hours. It can be given by continuous intravenous drip (0.1 mg. per c.c. with an average of 250 mg. per 24 hours) or

by intermittent i.v. injection (50 to 150 mg. in saline every 4-6 hours). The dosage is varied to keep the clotting time 2 to 3 times the normal determined before therapy is started. Thus clotting times are necessary every 6-12 hours. Due to its immediate action heparin is used where therapy is needed promptly. In myocardial infarction Green and Barsky and others (10) feel that anticoagulants are effective in preventing emboli which originate in the lower limbs and since this complication does not occur until after the first week, heparin is not indicated. However Richter, Munzie, and Swiller (11) state that in their series of cases treated with dicoumarol, 13 out of 15 cases which developed T.E. phenomena did so before therapeutic hypoprothrombinemia was produced, implying that rapid anticoagulant therapy was indicated.

(2) Depoheparin and Aqueous Intramuscular Heparin—To overcome the intravenous method of administration and to provide longer action two forms of heparin intended for intramuscular injection have been developed. Depoheparin is 200 mg. of heparin in a dextro-gelatin medium and the second form is a concentrated aqueous intramuscular heparin. Monkhouse, MacMillan, and Brown (12) studied both these agents and concluded that the heparin blood levels produced, the duration of the effect, and the average response of the clotting time, were the same for both agents. The maximum clotting time was reached in 4 hours and was 20 minutes. The duration of the effect was 8 to 12 hours. Friedberg (1) recommends that the initial dos-

age of depoheparin be 400 mg. and the maintenance dose be 200 mg. every 12 hours. The dosage of concentrated aqueous heparin varies with different authors. Some recommend a single dose of 25,000 units which is 250 mg. every 12 hours but most authors including Gubbay and Pash (13) recommend a dose of 6,250 units which is 63 mg. or one-quarter of a c.c.—every 4 hours. These same authors found that there is a delay of absorption and hence of action if the patient is in shock and thus prefer i.v. heparin when shock is present. Gubbay and Pash reported no complications or pain at the site of injection with these agents.

(3) Treburon—This is a new synthetic heparinoid with action similar to that of heparin. It can be given either intramuscularly or intravenously. Wright (5) used it intravenously and obtained a rapid prolongation of clotting time which lasted 3 to 6 hours—very similar to that of heparin. Field et al. (14) used a dose of 250 mg. intramuscularly and reported a rapid rise of clotting time reaching a maximum in 3 to 6 hours and remaining effective for 24 hours. However, these authors and others report severe toxic reactions in many cases including alopecia and severe diarrhea. Further experimentation is needed before this agent can be used in clinical medicine.

(4) Paritol—This is another synthetic which is similar to heparin in chemical structure and action. Wright (5) reports that an intravenous dose of 150 to 350 mg. acts in 5 to 10 min. and lasts for 8 to 12 hours. However, he, Friedberg (1) and others report that due to shock-like

states developed, this agent is too toxic for clinical use.

2. Oral Anticoagulants:—

(1) Dicoumarol — Dicoumarol is the oldest of the oral anticoagulants. It acts directly on the liver and depresses the prothrombin formation resulting in a prolongation of the prothrombin time. The question of toxic effects on the liver has often been discussed but it is the conclusion of Green and Barsky (10) that "there is no good evidence that this group of drugs can produce any permanent damage to the liver, nor, indeed, damage to any other organs". Dicoumarol has a latent period of about 24 hours before its hypoprothrombinemic effect begins and it takes about 48 to 72 hours before a therapeutic level of hypoprothrombinemia is reached. The effects of dicoumarol last from 3 to 8 days. This has been described as a disadvantage by some as it means that if bleeding occurs it takes several days before the effect of the drug wears off. On the other hand, the prolonged effect makes the drug useful for long term therapy. The initial dose is usually 200 to 300 mg. or can be based on weight when 5 mg. per Kg. of body weight is given. The maintenance dose varies with the prothrombin time but is usually between 50 and 125 mg. or 1.5 mg. per Kg. body weight. The maintenance dose can be given daily or by the intermittent method by which no more is given until the prothrombin time begins to fall and then another large dose is given. This latter method is preferred by some workers as it avoids the accumulation of the drug. During treatment, daily prothrombin times are essential

at least until the patient is stabilized, as hypo- and hyper-reactors are not uncommon. Most authors agree that the prothrombin time should be kept in the range of 20% to 40% of normal.

(2) Tromexan—This agent is a coumarol derivative and on comparison with dicoumarol the drug was given the following attributes by the Committee on Anticoagulants of the American Heart Association:—

1. Tromexan gives a more rapid prolongation of the prothrombin time.
2. The prothrombin returns more rapidly to normal when the drug is discontinued.
3. Its power to protect against thrombo-embolic phenomena is about equal to that of Dicoumarol.
4. As with dicoumarol the prothrombin time must be watched carefully.
5. The prothrombin time is more easily controlled if given in 2 or 3 divided doses daily. The initial dose varies from 1200 to 1800 mg. and it reaches its therapeutic level in about 18 to 36 hours. Its duration of activity varies from 2 to 6 days. The maintenance dose varies from 300 to 900 mg. daily, depending on the prothrombin time. On reviewing the literature almost all workers agree that it is very difficult to maintain stable levels of hypoprothrombinemia with this agent. Weiner, Simpson, et al. (15) report that prothrombin times showed considerable daily fluctuations even with divided doses and whether given orally or intravenously. All authors agree that there were no significant hematologic, renal, liver, or other toxic effects with tromexan.

(3) Cyclocoumarol—This agent is also a coumarol derivative. Cyclo-

coumarol has several advantages over both dicoumarol and tromexan. It has an earlier onset of action than dicoumarol and maintains its therapeutic effect for a longer period than either dicoumarol or tromexan. Rotter and Meyer (6) and Green and Barsky (10) report that it is easier to maintain a consistent hypoprothrombinemia with cyclocoumarol than with either dicoumarol or tromexan. Further, Rotter and Meyer state it can be used effectively in patients that are resistant to dicoumarol. These same authors have maintained two patients on cyclocoumarol for 6 months with weekly checks of prothrombin time most of which were in the desired range of 20% to 40% of normal. The initial dose varies from 50 to 160 mg. or 2 mg. per Kg. body weight. It reaches its therapeutic effect in 24 to 48 hours. The maintenance dose varies from 35 to 125 mg. or 0.5 to 1 mg. per kg. body weight, according to various authors. It maintains its effect for 8 to 12 days and thus the maintenance doses can be given only 2 or 3 times weekly according to the prothrombin level. No toxic effects have been reported. Several authors feel that this agent is the drug of choice for prolonged therapy.

(4) Phenylindanedione (Danilone or Hedulin)—This agent is not a coumarol derivative, differing from them in chemical structure. This agent produces its therapeutic effect more rapidly than dicoumarol and has a more rapid cessation of action. Blaustein and associates (16) and Townsend and associates (17) agree that the prothrombin time can be stabilized in a few days and fluctuations are minimal if given in divided daily doses. Blaustein found that he could maintain a consistent effect

with prothrombin times every 7 to 14 days once the patient was stabilized, the only disadvantage reported by these workers is that some patients are resistant to its effects. The initial dosage is determined on a weight basis by Blaustein—200 mg. if under 150 lbs. and 300 mg. if over 150 lbs., but other workers give an initial dose of 150 mg. to all patients. It reaches its therapeutic effect in 18 to 36 hours and maintains its effects for 2 to 4 days. The maintenance dose varies from 35 to 150 mg. daily and is usually given in two divided doses. No toxic effects have been reported.

Choice of Anticoagulants.

In the treatment of myocardial infarction one can use either heparin alone, a coumarol alone, or a combination of the two. Since it is desirable to continue therapy for several weeks, heparin with its frequent injections and numerous clotting time determinations seem impractical to use alone. Dicoumarol does not provide the prompt therapeutic effect which is desirable and thus does not provide efficient therapy, if used alone. Thus some authors recommend the use of one of the quicker acting coumarol derivatives alone, such as tromexan or danilone. However, even these require at least 18 hours to reach therapeutic effect. Some authors such as Green and Barsky (10) feel that an anticoagulant effect is not needed in the first few days and thus recommend the use of coumarol derivatives alone but others feel that T.E. phenomena can occur very soon after an infarction and thus recommend the use of a combination of heparin and a coumarol. If a combination is desired, either intravenous heparin or intramuscular heparin can be used, along with a longer acting agent when the prothrombin time

reaches a satisfactory level the heparin is discontinued. From a practical standpoint the combination of an intramuscular heparin along with a coumarol derivative or danilone seems to be the choice. Gilchrist (18) reports success with the following regime - heparin either intravenously or intramuscularly is started the moment the diagnosis is made, the dosage being 77 mg. every 6 hours. A coumarol is started at the same time and the heparin is discontinued when the prothrombin time reaches 35 seconds.

Long Term Anticoagulant Therapy

The duration of therapy varies with different authors, Gilchrist (18) continuing therapy for 28 days after the infarction or 21 days after the last T.E. complication whichever is the longer. Others, however, recommend that therapy continue until the patient is fully ambulant. Recently there are reports of long term therapy continuing for months or years. Shipiro (19) states that "in patients exhibiting coronary artery insufficiency and in whom it may be expected that thrombosis might be imminent, or in those subjects who have experienced one or more attacks of myocardial infarction and in whom an attempt has been made to prevent additional closure, it is believed worthwhile to render the blood hypocoagulable for prolonged periods extending into years". He states that coumarol is particularly suitable for long term therapy due to its consistent action especially if given by intermittent therapy which avoids overdosage. Others feel that danilone is the drug of choice. Once the prothrombin time and dose are stabilized, it is only necessary to check the prothrombin every 5 to 7 days with these agents. Friedberg (1) states that "the studies

this far, besides implying that the incidence of current myocardial infarction and mortality rate has been diminished, are chiefly of value in indicating that such anticoagulant therapy can be undertaken without undue risk".

Haemorrhage During Anticoagulant Therapy

Where one is using a drug to increase the clotting time of the blood, the danger of bleeding from overdosage is inherent in the nature of this agent. Dangerous bleeding occurring at therapeutic levels usually has some adequate explanation according to Green and Barsky (10). The presence of any blood dyscrasias, bleeding ulcers or other bleeding sites are contraindications to the use of anticoagulants. No surgical procedures such as spinal puncture, thoracentesis, or sympathetic block should be carried out while the patient is on these drugs. The occurrence of bleeding while on anticoagulants varies with different authors. Some report no haemorrhagic phenomena in their experience while others report as high as 15% of their cases have abnormal bleeding. Nichol summarized the experience of 136 physicians and reported that abnormal bleeding occurred in 2% of 15,500 cases and the mortality rate from haemorrhage was only 0.18%. Green and Barsky point out that where the prothrombin time is kept between 20% and 40% of normal, bleeding occurs in only 2% of cases but that when the prothrombin time is maintained at below 20% bleeding occurs in 10% of cases.

When bleeding occurs, definite measures can be taken to arrest it. The drug should be stopped at once of course, and no matter what drug is used transfusions of whole blood are

TABLE I

CONTROLS				TEST GROUPS		
Not treated with anticoagulants				Treated with anticoagulants		
Total No. of Cases	Number of Cases	Percentage mortality	Percentage T. E. phen.	Number of Cases	Percentage mortality	Percentage T. E. phen.
(1) 1030	442	23.4%	26%	589	16%	10.9%
(2) 311	211	32.0%	19%	100	18%	14%
(3) 455	148	49%	15.6%	156	19%	7.23%
(4) 300	150	33.3%	20%	150	11.3%	10%
(5) 1800	—	30.6%	21.8%	—	16.2%	9%
(6) 724	324	23.2%	19.4%	400	13%	9%

(1) H. I. Russek and B. L. Bohman—*Amer. Heart Jour.*—June, 1952.

(2) R. B. Turman, C. O. T. Ball, R. G. Gale, F. T. Billings—*Amer. Jour. of Med.*—June, 1953.

(3) R. L. Wooten, F. A. Keper—*Annals of Internal Med.*—February, 1953.

(4) I. H. Richter, R. F. D. Munzie, S. I. Swiller—*New York State Jour. of Med.*—May, 1953.

(5) A. R. Gilchrist—*Br. Med. Jour.*—August, 1952.

(6) E. S. Mills—*Can. Med. Assoc. Jour.*—January, 1953.

indicated if the bleeding is at all serious. With heparin, 50 to 100 mg. of a 1% solution of protamine sulfate I.V. will restore the clotting time to normal promptly. With the coumarol derivatives, vitamin K in doses of 70 to 100 mg. I.V. can be given or 10 mg. I.M. every 4 hours. Vitamin K oxide has been found to be better than vitamin K in some cases and this is given in doses of 1 gm. I.V.

New Theories on the Mode of Action of the Anticoagulants.

Though it is generally accepted that the anticoagulants are effective in reducing the mortality in myocardial infarction mainly by reducing the number of T.E. phenomena, many feel that these agents have other

beneficial effects which indicate their use. Gilchrist (18) states that patients on anticoagulants look and feel better than the control groups. He further concludes that his statistics show that the over-all reduction in mortality rate among those receiving treatment cannot solely be due to a decrease in frank T.E. deaths. They seem to reduce deaths from shock and may limit the spread of multiple thrombotic extensions in and through the zone of demarcation separating necrotic from healthy muscle. Turman and associates (4) conclude that the reduction in mortality is due to some property other than their anticoagulant effect. Green and Barsky (10) state that the coumarol drugs are effective vasodilators, and Mich-

TABLE II
COMPARISON OF VARIOUS ANTICOAGULANTS

DRUG	Time Required to Reach Therapeutic Effect	Duration of Activity	Initial Dose	Maintenance Dose	Route of Administration
Heparin	5 to 10 min.	4 to 5 hrs.	50-100 mg.	50-100 mg. q.6h.	I.V. Intermittent
Paritol	5 to 10 min.	8 to 12 hrs.	150-350 mg.	125-680 mg.	I.V.
Treburon	3 to 6 hrs.	10 to 24 hrs.	250-627 mg.	250-625 mg. q.12h.-24h.	I.M.
Depoheparin	2 to 4 hrs.	12 hrs.	400 mg.	200 mg. q.12h.	S.C.
Aqueous I.M. Heparin	2 to 4 hrs.	8 hrs.	40-50 mg.	40-50 mg. q.4h.	I.M.
Dicoumarol	48 to 72 hrs.	3 to 8 days	200-300 mg. or 5 mg/kg.	50-125 mg. or 1.5 mg/kg. daily	oral
Tromexan	18 to 36 hrs.	2 to 6 days	1200 to 1800 mg.	300-900 mg. daily	oral
Cyclocoumarol	24 to 48 hrs.	8 to 12 days	120-160 mg. or 2 mg/kg.	50-125 mg. or 0.5-1mg./kg.	oral
Danilone	18 to 36 hrs.	2 to 4 days	150-200 mg.	25-150 mg. daily	oral

Modified from C. K. Friedberg—C.M.A.J., February, 1953.

aelides and associates (20) state that E.K.G. studies showed that anticoagulant therapy either prevented or greatly limited ischemic lesions from appearing. According to McLetchie, (21) atheroma is due to the deposition and organization of multiple thrombi on the initial surface of the arteries and therefore concludes that long term anticoagulants are effective in preventing further atheroma from developing and thus preventing coronary occlusion.

Laboratory Control.

The importance of adequate laboratory control in the use of the anticoagulants cannot be too strongly emphasized. Indeed the absence of such laboratory control is an absolute contraindication to their usage.

When using heparin the most accurate method to determine the clot-

ting time, and indeed the only reliable one, is the Lee and White method which uses venous blood. The determination of the prothrombin time is usually done by the Quick method. In order to be accurate this test must be carried out carefully with due attention to all its details. There are certain points which need to be emphasized with regard to the determination of the prothrombin time. As the potency of the thromboplastin used in the laboratory determination may vary and thus affect the significance of the actual time in seconds, it is important that each time a test is performed the prothrombin time of a normal control plasma be also determined. It is important for the test to be performed on fresh plasma, for if it stands too long an apparently low prothrombin time will result. The plasma must be collected in a stan-

dard amount of oxalate, usually 0.5 c.c. Green and Barsky (10) report that false low prothrombin levels can result even when the test is performed accurately due to inhibiting substances in the blood and as a result a patient may be denied anticoagulants.

It is important for both the physician and the technician to be fully aware of the difficulties and pitfalls inherent in the determination of the prothrombin time when anticoagulants are used.

References:

1. C. K. Freidberg, "The Current Status of the Treatment of Coronary Artery Disease". C.M.A.J., Feb., 1953.
2. H. I. Russek, B. L. Zohman, A. A. Doerner, A. S. Russek and L. G. White—"Indication for Dicoumarol in Acute Myocardial Infarction Circulation", May, 1952.
3. D. Littmann—"The Prevention of Thrombo-Embolism in Acute Coronary Artery Disease" Digest of Treatment, January, 1953.
4. R. H. Turman, C.O.T. Ball, R.G. Gale, F. T. Billings, G. R. Meenley—"An Evaluation of Anticoagulant Therapy in Myocardial Infarction based on Prognostic Categories." Amer. Jour. of Med., June, 1953.
5. I. S. Wright—"An Evaluation of Anticoagulant Therapy." Amer. Jour. of Med., June, 1953.
6. R. Rotter and O. O. Meyer—"Further Experience in Coumarin Anticoagulants." J.A.M.A., Nov. 22, 1952.
7. L. Beaumont, H. Chevalier, J. Lenegree—"Studies on the Spontaneous Variations in Blood Coagulability following Myocardial Infarction" Amer. Heart Jour., May, 1953.
8. A. A. Fitzgerald Peel—Br. Heart Jour., May 1953.
9. J. A. Lewis—"Anticoagulants in Coronary Thrombosis". C.M.A.J., May, 1953.
10. P. T. Green and P. Barsky—"Anticoagulant Therapy". Treatment Services Bulletin, Feb., 1953.
11. I. H. Richter, R. F. D. Munzie, S. I. Swiller—"An Evaluation of the Dicoumarol Therapy in 300 Cases of Myocardial Infarction." N. Y. State Med. Jour., May, 1952.
12. F. C. Monkhouse, R. L. Mac Millan, W. G. Brown—"The Relation Between Heparin Blood Levels and Blood Coagulation Times". Jour. of Lab. and Clin. Med.
13. E. R. Gubbay, E. Pash—"Intramuscular Aqueous Heparin". C.M.A.J., Aug., 1953.
14. J. B. Field, G. D. Ramsey, A. M. Attyah, P. Starr—"The Effect in Man of a new Heparinoid, Theburon". Jour. of Lab. and Clin. Med., May, 1953.
15. M. Weiner, G. Simson, J. J. Burns, J. Murray Steele, B. B. Brodie—"Prothrombin Activity with Tromexan Therapy". Amer. Jour. of Med., June, 1953.
16. A. Blaustein, N. Shnayerson, R. Wallach—"Clinical use of a new Anticoagulant phenylindanedione". Amer. Jour. of Med., June, 1953.
17. S. R. Townsend, K. J. Fay, J. R. Downing, R. Laing, D. C. Cameron—"Phenylindanedione—A Useful Anticoagulant". C.M.A.J., Aug., 1953.
18. A. R. Gilchrist—"Coronary Thrombosis and its Response to Treatment". Br. Med. Jour., Aug. 1952.
19. S. Shiparo—"Long Term Anticoagulant Therapy". Med. Clinics of N. A. 1953.
20. G. Michaelides, H. Tseverenis, D. Avgoustakis—"The Anticoagulant Treatment of Myocardial Infarcts." Int. Med. Digest, Feb., 1953.
21. N. G. B. McLetchie, Professor of Pathology, Dalhousie University—personal communication.