1950

Heparin/pitkin menstrum in the management of coronary artery thrombosis

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HEPARIN/PITKIN MENSTRUUM IN THE MANAGEMENT OF CORONARY ARTERY THROMBOSIS

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SENIOR THESIS

PRESENTED TO THE COLLEGE OF MEDICINE

UNIVERSITY OF NEBRASKA

OMAHA 1950

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INTRODUCTION

Since the introduction of the use of anticoagulant drugs in the prevention and treatment of intravascular thrombosis, their employment in the management of patients with acute myocardial infarction has been of major interest to clinicians in their desire to reduce the expected high incidence of thromboembolic complications usually anticipated in patients with this condition. This discussion is concerned with the development of a form of practical administration of one of these anticoagulant drugs and its application in the management of acute coronary thrombosis. The peculiar characteristics of this form of administration which may be applied advantageously in coronary thrombosis will be discussed along with a report of such brief clinical trials as have been published up to the present time. A comparison of this drug and its new medium of administration, heparin/Pitkin menstruum, will be made with Dicumarol in an attempt to evaluate this method of application in light of clinical results already obtained with Dicumarol.

It is not meant that anticoagulant therapy should be instituted as a treatment to replace any of the drugs already used to produce sedation or overcome vasospasm

in acute coronary thrombosis, but is to be used as one of the procedures participating in a conjoint theraputic attack. An attack which is not only designed to alleviate the apprehension of the patient and sustain his already embarrassed coronary circulation, but also markedly reduce his chances of further complicating thromboembolic phenomena and actively prevent further extension of myocardial damage.

HEPARIN/PITKIN MENSTRUUM IN ANTICOAGULANT THERAPY

The original observations on the action of heparin occurred, quite by accident, in the course of an attempt to isolate thromboplastic substances from mammalian tissue. McLean(14), working in Professor William Howell's laboratory in Baltimore in 1916, found that the phosphotide cuorin, prepared from heart and liver, delayed the clotting of dogs' oxalated plasma and serum. He felt that this was not due to an error in technique as the successful isolation of cephalin and cuorin from the same tissue was identical with the exception of the end stage. This discovery at once aroused the interest of Professor Howell, who immediately set out to produce a stable preparation and determine the chemistry of the anticoagulant. He was able to isolate from the liver a phosphotide having anticoagulant properties which they called heparin(22) to indicate its origin from the liver.

The Connaught Laboratories in Toronto and the Caroline Institute in Stockholm did much to establish methods of isolation and purification, and to determine the chemical and physiological properties of this substance. The work of Jorpes(5) in Sweden has indicated that heparin is a mucoitin polysulfuric acid consisting

of equimolecular parts of glycuronic acid and acetylated glucose amine combined in ester form with sulfuric acid. The groups in the heparin molecule(1) responsible for its activity are not as such, for it can be shown that removal of sulfate, amino nitrogen or carboxyl groups cause almost complete disappearence of its activity. Hence, it is in the arrangement, for it has been shown that type substances containing any one of these groups possess anticoagulant activity approaching that of heparin. The most significant biochemical property of heparin is its ability to react with protein forming a stable salt.

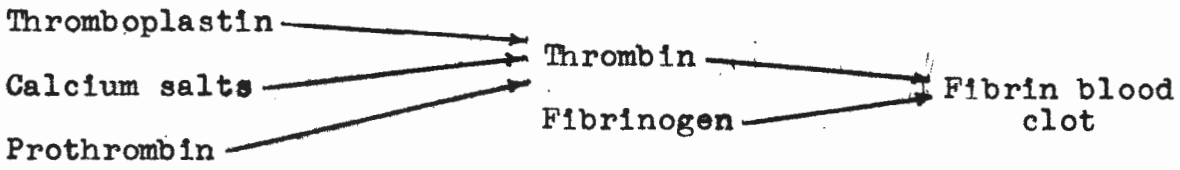
Although heparin was isolated from lung, spleen, kidney, etc., the lung was found to be a particularly rich source. It was noted by Jorpes(7) that the mast cell granules gave a similar staining with Toliudine blue as did heparin. Also, it was observed that there was a correlation between the number of mast cells in a given tissue and its heparin content. The abundance of these mast cells beneath the capsule of the liver, particularly around small blood vessels without muscle coats, coupled with the information gained through staining has led us to identify the liver as the principle site of origin of this substance.

There have been several theories concerning the

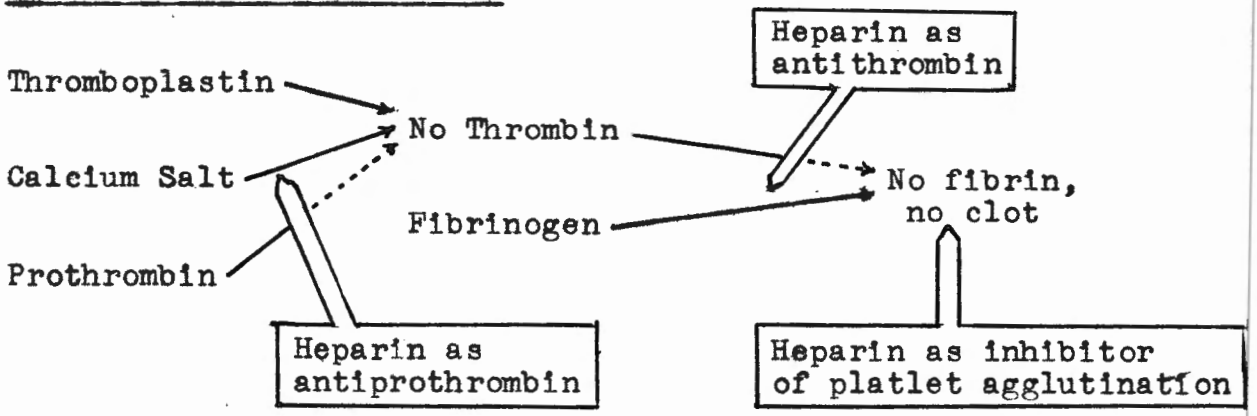
probable action of heparin. Howell (22) felt that heparin is an antiprothrombin which is normally present in the blood serving to stabilize prothrombin; also, that heparin activates a precursor of antithrombin. Quick also holds that heparin activates a precursor to antithrombin.

The action of heparin is well represented graphically in the following manner by Loewe(8):

NORMAL COAGULATION



MULTIPLE ACTION OF HEPARIN



It is of interest to note that minute guantities of heparin have been isolated from normal plasma but none from the serum of clotted blood.

From a physiological standpoint(10) the rational of heparin lies in the ability to prevent, with the aid of a plasma cofactor, the conversion of prothrombin into thrombin, to form a strong antithrombin in conjunction with the serum albumin and to prevent the formation of thromboplastin from platlets. Studies on the effect of heparin in experimental venous thrombosis(8) have revealed that red cell clots not organized and containing a minute amount of fibrin (sludge stage) disappear completely under heparin therapy. Heparin was also found to maintain patent adjacent collaterals and tributaries which ordinarily would become involved in the occlusive thrombotic process.

A review of literature indicates heparin has been used as an effective anticoagulant in a variety of conditions. A more widespread usage has been limited, however, by the necessity of administration only by continuous venoclysis or periodic intravenous injection. This is not practical in those cases requiring prolonged heparinization as it is both cumbersome and requires greater amounts of the drug to maintain theraputic blood levels.

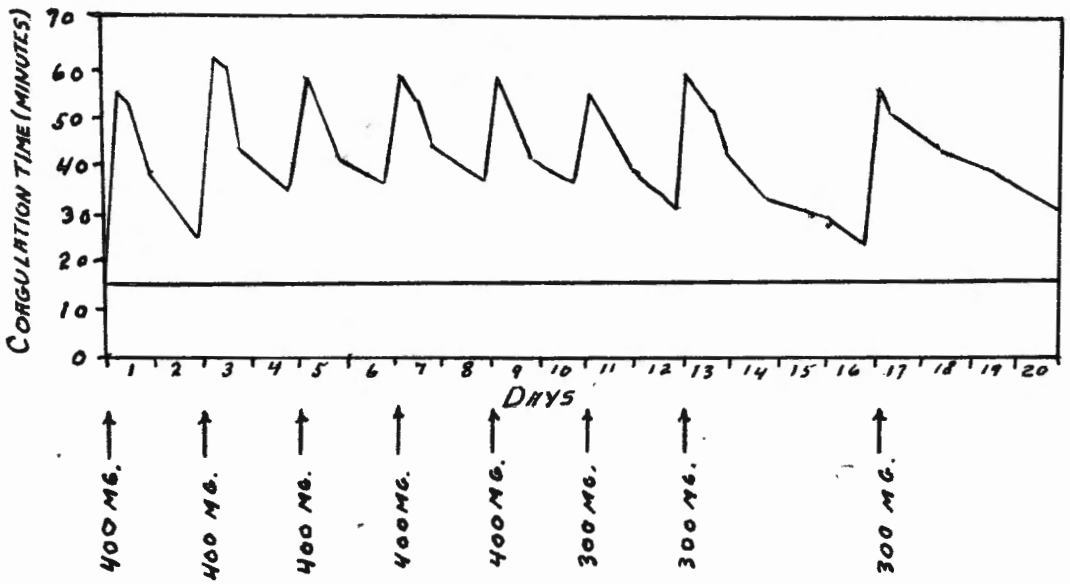
To accomplish a slow equable utilization by methods other than the intravenous, Loewe(6) adopted Pitkin menstruum as a vehicle for administration. This menstruum was developed to regulate the release of water soluble drugs injected intramuscularly or subcutaneously. The ingredients are: gelatin, 15 to 30 per cent; dextrose, 5 to 12 per cent; acetic acid, 1 to 1.5 per cent; distilled water, q. s. to 100 per cent. The viscosity of the menstruum, which is predicted on the concentration of the gelatin and dextrose, determines the rate of liberation of the drug; the greater the viscosity, the slower the liberation. In preparations containing heparin, the optimum percentages of gelatin and dextrose are 18 and 8 respectively. The mixture is prepared using aseptic precautions and placed in sterile ampules. Heparin and a vasoconstrictor are added at an elevated temperature; and the mixture is then sealed and allowed to cool. It may be prepared with or without the vasoconstrictor in the following proportions(10).

	With Vasoconstrictor		Without Vasoconstrictor	
Heparin sodium salt, mg.	300.0	200.0	300.0	200.0
Epinephrin hydrochloride, mg.	1.0	1.0	0	0
Ephredine sulfate, mg.	25.0	25.0	0	0
Chlorobutanol, mg.	0.5	0.5	0.5	0.5
Eucupin dihydrochloride, mg.	1.0	1.0	1.0	1.0
Pitkin menstruum, cc.	3.0	2.0	3.0	2.0

There is no alteration in the action of heparin administered by the menstruum. The major accomplishment has been that of a more convenient method of administration which is helpful in rendering the drug more useful, as difficulties of administration and control have prevented the profession from completely realizing the maximum benefits of anticoagulation therapy with heparin.

Any condition requiring anticoagulation therapy may be treated with heparin/Pitkin menstruum. To prepare the mixture for injection, the ampule is warmed until the contents are liquified and is thoroughly shaken to disperse any precipitated material. The contents of the ampule are drawn up through an 18 gauge needle into a 5 or 10 cc. syringe. The needle is then replaced by a 20 gauge needle and the injection is done immediately. The sites of injection are the deep subcutaneous (or superficial intramuscular) tissues, preferably on the anterior or lateral aspects of the thigh. It is preferable that injections be altered on either extremity to avoid an increase in the incidence of local complications. Body weight and individual reactivity dictate the amount of heparin/Pitkin menstruum to be used in a given case(21). For the initial injection, body weight may be employed as a guide. Patients weighing up to

200 pounds (90 Kilograms) should be given an initial dose of 400 milligrams of the heparin sodium salt. Subsequently, the dosage should be adjusted to the intensity of the "heparin effect" as estimated by the coagulation time. Compared to a normal coagulation time (Lee-White-Howell method) of 9 to 15 minutes, a coagulation time of 30 to 60 minutes is considered an adaquate "heparin effect". Subsequent dosage in a normal reaction appears to consist of injections of 400 milligrams of heparin without vasoconstrictor on alternate days for approximately one week, to be continued with 300 to 200 milligram injections as dictated by individual cases. The span of treatment is maintained until such time as the patient is permitted out of bed. Occasionally, patients who are on heparin therapy may, following abrupt withdrawal of the drug, develop a diphasic phenomena wherein the blood becomes hypercoaguable(6). This phenomena is obviated by a gradual decrease in heparin/Pitkin menstruum therapy. With the initial injection, there is a response in coagulation time within one to two hours and this is maintained for approximately forty eight hours. Following is an example(9) of a coagulogram in a normal reactor.



During the use of the earlier preparations, patients complained of local pain, swelling and tenderness at the injection site. This was found to be due to a precipitate resulting from the combination of heparin and eucopin. The pain induced by the precipitate was excessive, but could be controlled by adequate sedation. This objection has been overcome in subsequent preparations by means of careful buffering so that the pH of the gel is more physiologically acceptable and the tendancy to precipitate has been markedly lessened. Following the injection of a dose of 200 or 300 milligrams a patient will sometimes complain of palpitation and nervousness. These reactions are said by Loewe(9) to require no treatment, but will disappear in a short time. If suspension of activity is desired a small transfusion of whole blood, or relatively

fresh bank blood will inactivate any circulating heparin. The application of an ice bag or a tourniquet will suspend or slow up absorption into the blood stream.

Digitalis is said to inhibit the anticoagulant action of heparin. If possible its use should be avoided during a period of heparinization for it has been found(13) that theraputic doses of digitalis caused the clotting time to be accelerated in each of 24 patients during the administration of the drug. No changes have been observed in clot retraction or prothrombin time during digitalis administration. It has been suggested that digitaloid drugs have a thromboplastic effect on the clotting mechanism. Massive doses of pure heparin(12) have no toxic effect on the circulation, respiration, kidney and liver function, central nervous system or the neuromuscular behavior of animals. The effect of the vasoconstrictor drugs on heparin/Pitkin menstruum is one of prolonging the liberation of heparin from the site of injection by means of local vasoconstrictor effects. They should not be used in certain cases involving the thromboembolic phenomena where their transitory vasoconstrictor effects would be harmful, namely in the management of coronary artery thrombosis.

THE APPLICATION OF HEPARIN/PITKIN MENSTRUUM IN THE MANAGEMENT OF CORONARY ARTERY THROMBOSIS

In order to determine whether anticoagulant therapy would be of benefit in the management of coronary artery thrombosis, as well as in many other thrombotic conditions (6), it would seem desirable to know whether we can expect such patients to have accelerated coagulation times, and to what degree, if this be found the case. Furthermore, if such an acceleration can be demonstrated, it would be of benefit to know the expected duration of such a change. A group working at the University of Concinnati(17) has, using the extremely sensitive Waugh and Ruddick test, made such a determination. A total of 27 cases of coronary thrombosis were used and 16 controls, including 7 "normals" placed at strict bed rest for other reasons and 9 cardiac cases without myocardial infarction. Of the cases of coronary thrombosis 77.8 per cent showed the phenomena of accelerated coaguability at some point early in their hospital stay. Very commonly acceleration occurred by the third day and remained accelerated for several weeks. It was shown that the coagulative mechanism accelerated little from the normal during the first day of the attack and from the seventeenth day onward. This suggested that the clotting mechanism preceeding the

attack and after the third week did not differ from the normal.

It is the incidence of embolic or thrombotic processes during the immediate convalescence from acute myocardial infarction that justifies an attempt to prolong the coagulation of blood during the time. It was mentioned by Blumer(2) that mural thrombi were present over the surface of infarcted areas in approximately 50 percent of coronary occlusions and that embolism occurs in 14 percent of coronary occlusions. Nay and Barnes(16) report various other authors as having found 17 per cent to 66 per cent of necropsys following clinical evidence of myocardial infarction. Since the left ventricle is involved in virtually all instances of myocardial infarction, thrombi occur predominately in the left ventricle and whatever emboli arise from such thrombi effect the systemic circulation. Because of the frequency with which the intraventricular septum is involved both chambers are often found to contain mural thrombi. Emboli arising from right heart thrombi are, of course arrested in the lungs. To establish more significant data on incidence of thromboembolic complications in cases of coronary artery thrombosis uneffected by anticoagulant therapy Nay and Barnes(16) examined a series

of 100 cases of myocardial infarction using very rigid criteria for the occurrence of vascular complications. Of the 100 patients 37 per cent suffered from complications of a thrombolic or embolic nature. 28 per cent of the total group experienced only one complication, whereas multiple complications appeared in 9 per cent. The incidence of various thromboembolic complications found in this series is shown in the following table.

Total Complications in 37 cases:

Second myocardial infarction	15
Pulmonary embolism	14
Cerebral vascular accident	8
Thrombophlebitis	7
Peripheral artery occlusion	4
Total	48

The time of occurrence was noted to be of importance in this same series of 100 patients:

1. 87 per cent of the instances of a second myocardial infarction occurred between the 4th and 20th days.
2. 87 per cent of the cerebral accidents took place within the same period.
3. 86 per cent of the cases of thrombophlebitis began between the 10th and 16th days.

4. 93 per cent of the pulmonary embolism occurred between the 16th and 30th days, during periods at which blood pressures were at their lowest levels.

Since mural thrombi are more frequent after 48 hours and very rare before 24 hours following an acute coronary occlusion, it would seem that the earlier the institution of anticoagulant therapy the better.

The accelerated coagulation time occurs after tissue damage has been done and probably plays no role in the initiation of the original coronary artery thrombosis. However, once started, anticoagulant therapy tends to prevent further complications. We have, therefore, a fourfold objective in early institution of anticoagulant therapy(15): 1. The prevention of an extension of the thrombus, either proximally or distally to the original site of closure; 2. Prevention of the formation of intracardiac mural thrombi; 3. Prevention of thrombophlibitis from which pulmonary embolism may arise; 4. The prevention of thrombosis in the peripheral arteries already considerably effected by arteriosclerosis.

The original observations of the effect of an anticoagulant on the course of coronary thrombosis were made

by Soldant and Best(23) in 1937. They allowed sodium ricinoleate to remain in temporarily occluded coronary vessels of dogs and observed the occurrence of thrombo-embolic complications in a series of unheparinized and previously heparinized animals. Although their series included only 30 dogs, including controls, the results of their animal experiments were quite significant. The following year similar experiments(24) were done to determine the possibility of decreasing the incidence of artificially produced mural thrombi in animals. Again the results were exceedingly gratifying. These experimentors expressed the opinion that this might possibly work in humans. Since intra mural thrombi were found in a large percentage of coronary thrombosis cases, they believed heparin might be valuable in reducing the incidence of this complication. They felt called upon to answer the argument that anticoagulants were contraindicated in those cases involving subintimal hemorrhage with a statement to the effect that if such thrombi had already taken place heparin would have no effect. Furthermore, if given early, heparin would not increase the bleeding tendancy as subintimal hemorrhages at this location were always checked by pressure before clotting took place. In view of the excellent experimental results, further investigation of the coronary artery phase of heparin

therapy was advised. The effect of heparin on the clotting time of humans was subsequently investigated(15) and found to be a desirable one at such times as a prolongation of clotting time was indicated. Heparin therapy soon became a valuable aid in combating intravascular clotting.

Prior to the adoption of heparin/Pitkin menstruum, the methods of administration of heparin were limited mainly to multiple intravenous injection or continuous drip. The high cost of the drug at this time coupled with the technical difficulties in administration made its use relatively impractical in acute coronary thrombosis. These difficulties included the inconvenience of continuous intravenous administration, which was uncomfortable to an already apprehensive patient, and the necessity of constant vigil to prevent overheparinization and insure adequate blood levels. Also attempts at injecting of aqueous heparin subcutaneously(20) required unreasonably large amounts to maintain desired levels. The use of Dicumarol had become widespread by the time heparin/Pitkin menstruum had been developed and subjected to clinical trials.

The diagnosis of coronary artery thrombosis is an indication for the immediate institution of anticoagulant therapy, for maximum benefits are obtained by means of

prevention of further complications that would invariably appear in a certain number of unprotected cases. The duration of symptoms in a recent series of cases reported by Loewe(9) varied from 3 hours to 56 days before heparin/Pitkin menstruum was given. Once the diagnosis is established, it is important to achieve prompt anticoagulant response. Therefore, the initial dose of heparin in the menstruum should be at least 400 milligrams administered subcutaneously in the previously described manner. It is essential to use the preparations without the vasoconstrictor. It has been recommended(8) that the Lee-White-Howell method be used in estimation of all coagulation times. For effective heparinization the blood coagulation time should not be less than three times the control value; that is, 30 to 45 minutes as contrasted to a control coagulation time of 9 to 15 minutes. Prolongation of the coagulation time is followed and, after a pattern of responses has been ascertained, subsequent injections are more or less routine. The span of treatment must be continued until the patient is permitted out of bed and the heparin/Pitkin menstruum is then gradually withdrawn. If it is desirable these patients may be maintained on a prophylactic program of small doses of heparin for an indefinite period of time. This is considered in order, as these people presumably

have an inherent clotting tendency and are subject to recurrent episodes of thrombosis. There appears to be a direct correlation between the mass and extent of the thrombus and the degree of response to heparin; as the clot disappears, the individual becomes less resistant and more responsive to the anticoagulant. As a result, patients requiring 300 to 400 milligrams of heparin every other day eventually have, where there are no longer any detectable evidence of the persistance of the thrombus, been maintained in a protected state on as little as 100 milligrams of heparin in the Pitkin menstruum deposited every second to seventh day or longer. The outcome of this type of prophylactic therapy has not yet been reported in medical literature.

Clinical trials using heparin/Pitkin menstruum as the sole anticoagulant in the management of coronary artery thrombosis have been limited, but highly encouraging. Of 6 cases of uncomplicated coronary artery thrombosis treated within 24 hours of the onset of symptoms there was complete recovery from the attack in all cases, whereas the mortality of an unprotected group is 20 to 30 per cent. Loewe(9) realized that this was inconclusive, but highly suggestive, because of the small number of cases treated. A slightly larger group, 20 in number, including those patients with complication thromboembolic phenomena,

showed a mortality of only 5 per cent. In none of the remaining 95 per cent was there reported evidence of extension of the preexisting thrombi whether arterial, intracardiac or venous, once heparin/Pitkin menstruum injections were begun. All existing thromboembolic processes were terminated promptly. When heparin/Pitkin menstruum was inaugurated early there was a more rapid clinical and electrocardiographic regression. In optimally treated patients, the convalescence was accelerated and the patients were restored more rapidly to their accustomed activities.

The use of heparin in conjunction with Dicumarol has been reported as a successful procedure by Glueck (4), Parker and Barker(19). Here heparin was used to gain prolongation of prothrombus time until Dicumarol given orally had produced its full effect. Parker and Parker were of the opinion that heparin administered subcutaneously was too difficult to control. No further explanations were offered to give a clue to the exact nature of the subcutaneous administration used on these patients. Because the full effect of heparin in the menstruum is reached within 1 to 2 hours and diminishes gradually over a period of approximately 48 hours, it seems reasonable to believe(6) that adequate anticoagulant blood levels could be maintained by a single injection of

heparin/Pitkin menstruum until the action of simultaneously administered Dicumerol comes into play. This action may, in some measure, gain a few of the advantages of both of these preparations.

The only other anticoagulant than heparin to receive recognition in the management of coronary thrombosis has been Dicumarol. Before the advent of a method of practical subcutaneous injection of heparin, Dicumarol proved to be the more popular, not due to the pharmacological qualities of the drug itself, but because of the availability and ease of administration. In view of the alterations made in the mode of heparin anticoagulant therapy made by the Pitkin menstruum, one may now draw a more even comparison to point out the advantages and disadvantages of both heparin/Pitkin menstruum and Dicumarol in reference to coronary thrombosis in order to determine where each can be best used. With regard to dosage, that of heparin/Pitkin menstruum is usually 400 milligrams initially and varies little, while that of Dicumarol is more completely dependent on Prothrombin determinations. Control of the heparin may be maintained by bedside coagulogram as compared to the prothrombin determinations used for Dicumarol. For the condition requiring early anticoagulant response, that of heparin/Pitkin menstruum is within 1 to 2 hours and is quite constant

and predictable(9). The response to Dicumarol occurs within 24 to 48 hours and is not as predictable, but can be managed by careful regulation of the individual dosage schedule. The administration of Dicumarol is advantageous from this point of view except in comatose patients. Although both drugs are contraindicated when there is active bleeding, additional contraindications to the use of Dicumarol are renal disease and hepatic disease. Hemorrhage is complication of overdosage of Dicumarol; this has not been known to occur during the administration of heparin/Pitkin menstruum where there is an intact cardiovascular system. Interruption of Dicumerol therapy may be accomplished by means of fresh whole blood transfusion or by massive doses of Vitamin K intravenously. There is a certain possibility in the latter of reinducing the thrombosis(3). Intravenous protamine, small whole blood transfusion or simply an ice bag to the site of injection will bring about cessation of the effect of heparin in the Pitkin menstruum(8). As to the matter of cost, at this time Dicumarol is much less expensive. This no doubt helps account for its relative popularity. It is to be hoped that the cost of heparin/Pitkin menstruum will be decreased in time to such an extent that this will cease to be a factor in the choice of drugs for anticoagulant therapy. Physicians have apparently met with approximately

equal success in both as applied to coronary artery thrombosis although the results obtained with Dicumarol have been more extensively published. From such a comparison, as made above, it becomes apparent that the low cost, ease of administration, relative difficulty of control, slow action, and possible complications of Dicumarol must be weighed against the relatively high cost, slightly more difficult administration, quicker action, easier control, and freedom from danger of serious complications of heparin/Pitkin menstruum in determining their exact course of anticoagulant therapy with reference to coronary thrombosis.

SUMMARY

The nature of heparin/Pitkin menstruum has been discussed with reference to composition and pharmacological properties. In considering the use of heparin/Pitkin menstruum in general anticoagulant therapy, the indications, for the institution of treatment, technique of implantation, dosage schedules, control, and toxicity were described. It was observed that the menstruum allowed the production of a prolonged "heparin effect" thus eliminating the inconveniences under previous intravenous and subcutaneous methods of administration. Reactions and complications, such as hemmorrhage and pain, were found to be rare and of little significance. Immediate cessation or lessening of the effect of heparin in the Pitkin menstruum when required, were noted to have been accomplished simply and easily.

In the consideration of coronary thrombosis, the rational substantiating the use of heparin/Pitkin menstruum included the prevention of mural thrombi, pulmonary embolism, subsequent coronary thrombosis, and peripheral vascular thrombi during the period following a given attack. The method described here allows the specific benefits of heparin to be utilized without the inconvenience of intravenous administration. In a small

series of 20 severe cases of coronary thrombosis, excellent results were found to have been obtained, only one death having occurred. This compared very favorably with similar cases which had received no anticoagulant therapy. These 20 patients are now being continued on small maintenance doses of heparin/Pitkin menstruum. The outcome of this prophylactic therapy remains to be determined in the future. Heparin/Pitkin menstruum and Dicumarol were compared with regard to their application in the management of coronary thrombosis. The heparin preparation appeared to be more expensive, more difficult to administer, less liable to complications, easier to control, and quicker acting than Dicumarol. This latter quality is felt to be of special benefit in cases where an early anticoagulant effect is desired, as is the situation in the management of coronary artery thrombosis.

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