Heparin and Warfarin: Use of Anticoagulants in the Prevention and Treatment of Venous Thrombosis and Pulmonary Embolism

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The physician frequently encounters the problems of deep vein thrombosis and pulmonary embolism. Recently, a number of studies have been published which are of considerable help in the management of these disorders. It has been shown that in many cases, low-dose heparin is effective in the prevention of both venous thrombosis and pulmonary embolism. However, once venous thrombosis has already occurred, it is necessary to use full-dose heparin, preferably by the continuous intravenous route, with maintenance of the partial thromboplastin time (PTT) at 1½ times the control at all times. Although monitoring the PTT may not prevent hemorrhage, it will help prevent further thrombosis. Heparin is generally continued for seven to ten days. During this time warfarin is generally begun, and it is important to continue the patient on warfarin for five to seven days while the patient is receiving intravenous heparin therapy. After stopping heparin, oral anticoagulation with warfarin should be continued for six weeks. Then, in the absence of a previous history of venous thromboembolism or a known predisposing condition, it is safe to abruptly discontinue anticoagulation in most patients.

Venous thrombosis and pulmonary embolism are problems frequently encountered by the physician. Recently much attention has been focused on both the prevention and definitive treatment of these disorders. However, there continues to be much confusion over low vs high dosage of heparin, length of therapy, and many other aspects of heparin and warfarin usage. This brief article is designed to summarize the current state of knowledge and to address several key questions by reference to a number of recent studies.

The following questions will be addressed regarding anticoagulant therapy: (1) What is the mechanism of action of heparin? (2) What is the rationale behind the use of low-dose heparin? (3) What is the evidence that low-dose heparin is effective in preventing venous thrombosis and pulmonary embolism? (4) Who should receive low-dose heparin therapy? (5) Is continuous heparin preferable to intermittent heparin in full anticoagulation? (6) For prevention of recurrent deep vein thrombosis, how high should the partial thrombo-

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plastin time (PTT) be? (7) Will control of the PTT prevent hemorrhage? (8) What is the correlation between the PTT, the Lee-White clotting time, and plasma heparin assay? (9) After pulmonary embolism treated initially with heparin and followed by warfarin, how long should warfarin be given before it is safe to discontinue the heparin? (10) In a patient being treated with both heparin and warfarin, how can the anticoagulant effect of warfarin alone be determined? (11) After acute deep vein thrombosis or pulmonary embolism, how long should oral anticoagulation be continued? (12) Is it safe to abruptly discontinue oral anticoagulation?

Literature Review

The exact mode of action of low dose heparin prophylaxis is not completely defined. However, much information is available regarding the effect of heparin on the coagulation mechanism, and from this information it can be seen how heparin in low dose could theoretically prevent thrombosis, whereas much higher doses are necessary once thrombosis has actually occurred. Heparin acts by binding to a plasma protein, antithrombin III, markedly enhancing the ability of this protein to neutralize various clotting factors.[1] In particular, there is an extremely high affinity of the antithrombin-heparin complex for factor Xa. The enzymatic coagulation system acts as a biological amplification system, and inhibition of small amounts of factor Xa blocks the formation of large amounts of later reaction products (Figure 1). For example, it has been shown that 1 μg of antithrombin III will inhibit 32 units of Xa, which in turn prevents the generation of 1,600 units of thrombin.[2] Thus, it seems reasonable that in order to interfere with the coagulation system at an earlier stage, smaller doses of heparin would be required than if thrombin had already been generated. Once venous thrombi are present, it becomes necessary to specifically neutralize thrombin; for this purpose low-dose heparin is inappropriate, and much higher doses of heparin must be used.

With this understanding of the impact of small doses of heparin, it is not surprising that since 1971, more than 20 trials of low-dose heparin in surgical patients have demonstrated, with only one exception, that there is a significant decrease of deep vein thrombosis in the treated compared to the nontreated groups.[3] However, acceptance of the use of low-dose heparin was delayed until it could be shown that in addition to reducing deep vein thrombosis, it significantly reduced the incidence of pulmonary embolism. In 1975, Kakkar and associates organized a large study involving 4,121 patients over the age of 40 years who were undergoing a major abdominal or thoracic procedure.[4] In this study, there was a significant decrease in postoperative deaths due to pulmonary embolism in the group treated with low-dose heparin. Although the treated group had a greater incidence of wound hematomas, there was no increased risk of serious hemorrhage in this group as compared to the group receiving no heparin. In conclusion, the authors of this study claimed that low-dose heparin prophylaxis "is highly effective in preventing postoperative fatal pulmonary embolism. It is well tolerated by the patient, and requires no laboratory control to regulate the dosage. . . .This form of prophylaxis against venous thromboembolism can now be recommended for use on a large scale in high-risk patients undergoing major surgery." Currently, low-dose heparin prophylaxis is recommended for patients over 40 years of age undergoing major surgery with the following exceptions: major orthopedic procedures (especially of the hip), open prostatectomy, and in brain or eye surgery.[5-7] Low-dose heparin has not been proven to be uniformly effective in major orthopedic or prostatic surgery. In neurosurgical or ophthalmological procedures, no increased oozing of blood either operatively or postoperatively can be tolerated.

The recommended dose for prophylaxis with low-dose heparin is 5,000 units of heparin administered two hours prior to surgery and repeated every 8 to 12 hours thereafter, until the patient is ambulatory.[6] Heparin comes in various concentrations, from 1,000 units/ml to 40,000 units/ml. The concentrated form of either 20,000 or 40,000 units/ml is generally preferred for low-dose prophylaxis, and should be injected subcutaneously in the abdominal wall with a small, 25 to 26-gauge needle.

Very few trials of low-dose heparin have been conducted in nonsurgical patients, and all of these have been in patients with acute myocardial in-

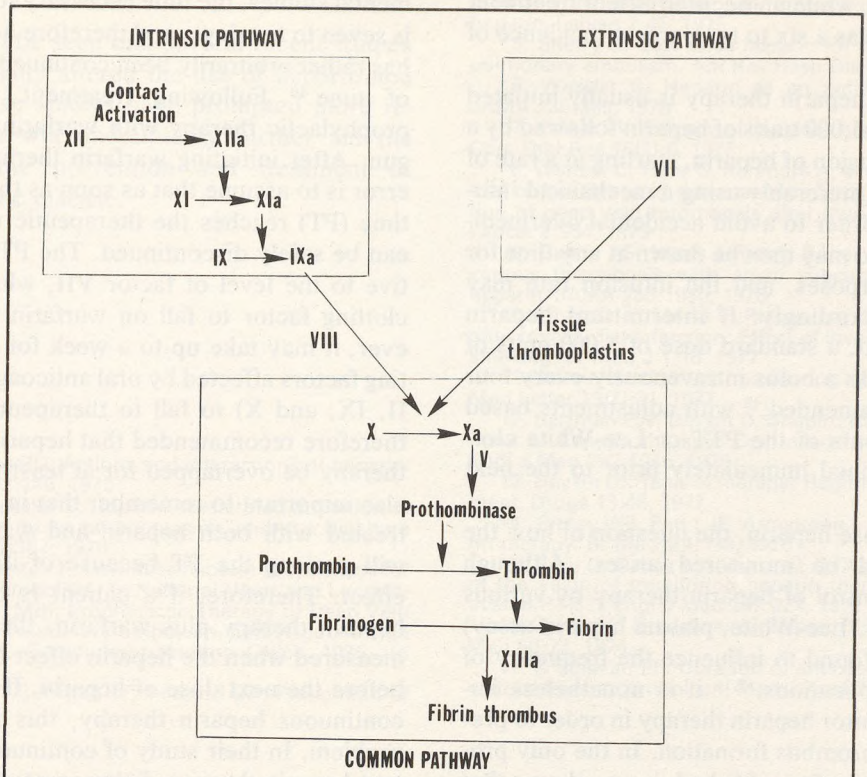

Figure 1. Simplified diagram of the coagulation system. Heparin acts by binding to a plasma protein, enhancing the ability of this protein to neutralize several of the clotting factors, especially factor Xa. The use of relatively low doses of heparin to inactivate a small amount of Xa prevents the formation of much larger amounts of thrombin

farction. These studies indicate a significant decrease in the incidence of deep vein thrombosis,[8-10] but no data are available regarding the effect on pulmonic or systemic emboli.

Low-dose heparin is useful in preventing the initial occurrence of thrombosis. In patients who already have active thrombosis or pulmonary embolism, full-dose heparin, usually by the intravenous route, is necessary to prevent further thrombus formation. Continuous heparin infusion is generally preferable to intermittent intravenous injection.[11] In a controlled prospective trial, although there was no significant difference in the number of thromboembolic complications between the two groups, major bleeding complications (including wound hematoma, intracranial bleeding, hemothorax, hemarthrosis, and soft tissue hematoma) were seven times greater in the intermittent than in the continuous groups.[12] In the continuous treatment groups, there was a one percent incidence of

major bleeding, while in the intermittent treatment groups, there was a six to ten percent incidence of major bleeding.

Continuous heparin therapy is usually initiated with a bolus of 5,000 units of heparin followed by a continuous infusion of heparin, starting at a rate of 1,000 units/hr (preferably using a mechanical infusion pump in order to avoid accidental overmedication).[13] Blood may then be drawn at any time for monitoring purposes, and the infusion rate may be altered accordingly. If intermittent heparin therapy is used, a standard dose of 5,000 units of heparin given as a bolus intravenously every four hours is recommended,[13] with adjustments based on measurements of the PTT or Lee-White clotting time obtained immediately prior to the next injection.

With full-dose heparin, the question of how the patient should be monitored arises. Although monitoring control of heparin therapy by various methods (PTT, Lee-White, plasma heparin assay) has not been found to influence the frequency of bleeding complications,[12,14] it is nonetheless important to monitor heparin therapy in order to prevent further thrombus formation. In the only prospective study so far published, it was shown that recurrence of venous thromboembolism is rare if the PTT is maintained at $1^1/_2$ times the control at all times.[15] It is important to recognize that the therapeutic level is based on normal controls rather than on the patient's baseline, which may be accelerated due to active thrombosis. If the Lee-White clotting time is used instead of the PTT, experimental studies have shown that in order to prevent thrombus formation, it should be prolonged to two or three times that of normal controls (usually a prolongation to at least 25 to 30 minutes).[16]

It is of interest to note that a study performed by Pitney[14] in 1970 shows that there is little correlation among the various laboratory tests commonly used to monitor heparin therapy, ie, PTT, Lee-White clotting time, and heparin assay. Correlation coefficients between any two of these tests were calculated to be approximately 0.6, with 0.0 representing no correlation and 1.0 representing a perfect correlation. Thus, it is impossible to predict accurately any one of these laboratory tests based solely on the results of one of the others.

Continued thrombosis may occur until the thrombus has been endothelialized. In experimental studies, the time necessary for this to occur is seven to ten days, and therefore heparin therapy has rather arbitrarily been continued for this length of time.[16] Following treatment with heparin, prophylactic therapy with warfarin is usually begun. After initiating warfarin therapy, a frequent error is to assume that as soon as the prothrombin time (PT) reaches the therapeutic range, heparin can be safely discontinued. The PT is very sensitive to the level of factor VII, which is the first clotting factor to fall on warfarin therapy; however, it may take up to a week for the other clotting factors affected by oral anticoagulants (factors II, IX, and X) to fall to therapeutic levels. It is therefore recommended that heparin and warfarin therapy be overlapped for at least five days. It is also important to remember that in a patient being treated with both heparin and warfarin, heparin will prolong the PT because of its antithrombin effect. Therefore, if a patient is on intermittent heparin therapy plus warfarin, the PT should be measured when the heparin effect is minimal, just before the next dose of heparin. If a patient is on continuous heparin therapy, this is not really a problem. In their study of continuous vs intermittent heparin therapy, Salzman et al[12] showed that (1) heparin had a minimal effect on the PT when the PTT was within the therapeutic range, and (2) after heparin was discontinued in patients receiving warfarin, the dose of warfarin required for adequate anticoagulation did not increase.

There is much uncertainty about how long oral anticoagulation should be continued, and frequently treatment is continued for many months or even years. A recent study[17] has shown that unless there is some other indication (such as a past history of venous thromboembolism, or a predisposing condition such as pregnancy, malignant disease, or cardiopulmonary disease), there is no evidence that patients receiving oral anticoagulants for six weeks have an increased incidence of deep vein thrombosis or pulmonary embolism as compared to patients receiving them for six months. It was also found that with abrupt cessation of oral anticoagulation therapy, there is not an increased incidence of recurrent venous thromboembolism. The author of this study concludes, "Unless there is some other indication, oral anticoagulation therapy for a period of six weeks would seem to be adequate for the majority of patients experiencing a single episode of venous thromboembolism."

Comment

Thus, it can be seen that several recent studies have substantially altered the use of heparin and warfarin. These studies have prompted more research, which will undoubtedly further aid the clinician in the prevention and treatment of thromboembolic disease.

References

1. Rosenberg RD: Actions and interactions of heparin. N Engl J Med 292:146, 1975
2. Yin ET, Wessler S: Heparin-accelerated inhibition at activated factor X by its natural plasma inhibitor. Biochem Biophys Acta 201:387, 1970
3. Hirsh J, Genton E: Low dose heparin prophylaxis for venous thromboembolism. In National Heart and Lung Institute (Bethesda, Md): Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism. DHEW publication No. (NIH) 76-866. Government Printing Office, 1975, pp 183-206
4. Kakkar VV, Corrigan TP, Fossard DP: Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Lancet 2:45, 1975
5. Sherry S: Low dose heparin for the prophylaxis of pulmonary embolism. Am Rev Resp Dis 114:661, 1976
6. Wessler S: Heparin as an antithrombotic agent. JAMA 236:389, 1976
7. Kakkar VV: Efficacy of low dose heparin prophylaxis. Curr Ther Res 18(1):6, 1975
8. Warlow C, Terry G, Kenmure A, et al: A double blind trial of low doses of subcutaneous heparin in the prevention of deep vein thrombosis after myocardial infarction. Lancet 2:934, 1973
9. Gallus AS, Hirsh J, Tuttle RJ, et al: Prevention of venous thrombosis with small subcutaneous doses of heparin. JAMA 235:1980, 1976
10. Emerson P, Marks P: Preventing thromboembolism after myocardial infarction: Effect of low dose heparin and smoking. Br Med J 1:18, 1977
11. Administration and monitoring of heparin therapy. Med Letter 19(7):31, 1977
12. Salzman EW, Deykin D, Shapiro RM, et al: Management of heparin therapy: Controlled prospective trial. N Engl J Med 292:1046, 1975
13. Deykin D: Heparin therapy: Regimens and management. Drugs 13:46, 1977
14. Pitney WR, Pettit JE, Armstrong L: Control of heparin therapy. Br Med J 4:139, 1970
15. Basu D, Gallus A, Hirsh J, et al: A prospective study of the value of monitoring heparin therapy with the activated PTT. N Engl J Med 287:324, 1972
16. Genton E: Guidelines for heparin therapy. Ann Intern Med 80:77, 1974
17. O'Sullivan EF: Duration of anticoagulant therapy in venous thromboembolism. Med J Aust 2:1104, 1972