VASCULAR SURGERY

Published six times a year under the auspices of

THE ANGIOLOGY RESEARCH FOUNDATION, INC.

Volume 16 January/February 1982 Number 1

Management of Anticoagulant and Thrombolytic Agents in Deep Venous Thrombosis

William W. Coon, M.D.

ANN ARBOR, MICHIGAN

Introduction

The presence of deep venous thrombosis involving the veins of the legs, pelvis, and vena cava or axillary and subclavian veins is an emergency situation, requiring immediate therapy. This presentation is confined to a brief discussion of the clinical utilization of antithrombotic agents in the management of this condition and its sequelae. Certain ancillary measures which are an integral part of treatment of deep venous thrombosis (limb elevation, elastic support) or pulmonary emoblism (respiratory support, vasopressors, antiarrhythmic drugs, etc.) are well known and have been discussed elsewhere.[1]

Heparin

Heparin has been the agent of choice for the initiation of therapy for venous thromboembolism. The selective use of a thrombolytic agent will be discussed in a subsequent section.

Recent pharmacologic studies have demonstrated that heparin is a heterogeneous mixture of active and inactive fractions of a sulfated mucopolysaccharide varying in molecular weight from 6,000–25,000; however, there is no evidence that commercially available products differ in antithrombotic potency if dosage is prescribed in heparin units. The anticoagulant effect of heparin is dependent upon its "activation" of antithrombin III, an α-2 globulin present in normal plasma. Heparin acts to accelerate the rate of

From the Department of Surgery, University of Michigan Medical Center, 1405 East Ann Street, Ann Arbor, Michigan 48109.

complexing of antithrombin with various serine proteases (thrombin and factors IX, X, XI, XII), thus inhibiting the normal process of blood coagulation. In patients with extensive intravascular thromboses, much larger than usual doses of heparin are occasionally required to achieve a predetermined level of anticoagulation; this may be related to the release of increased amounts of an antiheparin factor from platelets (platelet factor 4) involved in the thrombotic process.

The demonstration that the anticoagulant half-life of heparin in circulation is less than 2 hours in normal subjects and patients with venous thrombosis and even shorter in patients with pulmonary embolism has made continuous IV infusion the preferred method of administration. In addition to maintaining a more constant blood level of heparin, two recent prospective trials[2, 3] comparing continuous infusion with intermittent IV injection have shown that lesser amounts of heparin are needed with continuous infusion to maintain an adequate degree of anticoagulation and that hemorrhagic complications are appreciably less than with "pulse" injection.

When continuous infusion is utilized, direct IV injection of a loading dose of 3000–6000 units of dilute aqueous heparin is given before the infusion is started. A constant rate of infusion is maintained by use of an infusion pump. If a pump is not available, a pediatric burette, filled with a specific volume of heparin solution at hourly intervals, is a satisfactory alternative. In patients with venous thrombosis alone, the initial rate of administration of heparin is 1200 units/hour; in patients with pulmonary embolism, 1700 units/hour are infused. After approximately 3 anticoagulant half-lives (4–6 hours), the circulating blood level should have stabilized and can be monitored with an appropriate clotting test; the rate of infusion is adjusted if satisfactory anticoagulation has not been obtained.

If continuous infusion of heparin is not feasible, intermittent IV injection of dilute aqueous heparin (1000 units/ml) in a dose of 5000–6000 units every 4 hours is a satisfactory alternative which has been linked with a very low frequency of recurrent thromboembolism during therapy.[2] A heparin "well" (a small-caliber, butterfly-type of needle connected by a plastic catheter to a rubber diaphragm) can be utilized to lessen discomfort from repeated injections; from a pharmacokinetic standpoint, injections every 2 hours would be more desirable, but this doubles the workload of nursing staff. The total daily dose of heparin is usually in the range of 30,000–40,000 units if this method is used.

Although SC injection of aqueous concentrated heparin (20,000–40,000 units/ml) at 8–12-hour intervals has been utilized for many years for prophylaxis and treatment of selected ambulatory patients, its comparative efficacy in the management of acute venous thromboembolism has not been assessed.

Monitoring of the level of anticoagulation by one of several laboratory tests is essential. Although the use of coagulation tests in patients receiving intermittent IV injections of heparin may not lessen the frequency of hemorrhagic complications, there are data to show that maintenance of a given level of anticoagulation (an increase in activated partial thromboplastin time, thrombin clotting time, or Lee-White clotting time to 2–3 times normal) will lessen the frequency of thromboembolic complications.

The most widely used tests for regulating heparin therapy are the activated partial thromboplastin time (APTT) or the thrombin clotting time (TCT). A common problem in the use of these tests is failure to properly standardize the procedure by testing with varying concentrations of heparin in vitro. This is particularly important when the APTT is used since the "partial thromboplastin" reagents used in this test vary from laboratory to laboratory and some reagents (e.g. ellagic acid) lessen the sensitivity of the test to heparin. Monitoring of intermittent IV heparin therapy should be performed about 1 hour before the next injection and is repeated at daily or more frequent intervals to ensure that a cumulative increase in heparin level is not present and also that dosage is adequate.

Bleeding during heparin therapy is more frequent in elderly patients, particularly females, and in individuals with recent operations, ulcerative lesions, or hemostatic abnormalities. Special caution should be taken to ensure that that the subject is not receiving any drugs affecting platelet function. A recent concern are reports of occasional heparin-induced thrombocytopenia. Controversy exists concerning the frequency of this complication. In our experience and that of others,[4, 5] a significant reduction in platelet count is rare but, since this complication does occur, periodic platelet counts are desirable.

Oral Anticoagulants

Treatment with oral anticoagulants should accompany and supplement heparin therapy in all patients with major venous thromboembolism who have no serious contraindications to such treatment, are cooperative, and live in an area in which reliable laboratory control is available. Orally administered anticoagulants (coumarin or indandione derivatives) antagonize the action of vitamin K which is necessary for the γ-carboxylation of glutamic acid residues of the vitamin K-dependent clotting factors II, VII, IX, and X. The result is the synthesis by the liver of dysfunctional forms of these clotting factors which are no longer able to bind the calcium ions necessary for subsequent phospholipid binding and clotting factor activation. This effect is not immediate; effective anticoagulation occurs only after depletion of circulating functional vitamin K-dependent clotting factors. The maximum

depression of clotting factor activity occurs only after 5–7 days of administration. Since the optimal antithrombotic effect is achieved only after this interval, both heparin and oral anticoagulant administration should overlap over a period of 1 week.

Although the clinical significance of several laboratory findings has not yet been assessed, oral anticoagulant therapy should probably be initiated during the first week of treatment with heparin. Several investigators[6, 7] have reported that heparin therapy results in a progressive decrease in antithrombin III. Since warfarin appears to sustain or elevate antithrombin III levels in blood,[8] the early administration of oral anticoagulant might prevent some of the thrombotic complications observed after heparin therapy.[7]

While heparin therapy is maintained, the oral anticoagulant may be administered daily in an anticipated maintenance dose (e.g. 10–15 mg of warfarin); this avoids the occasional excessive anticoagulant effect observed when larger loading doses are given. At the end of 1 week, the expected therapeutic range of 20–30% prothrombin activity with the 1-stage prothrombin time should be achieved. Since individual patients exhibit as much as 10-fold variability in dosage requirements, daily laboratory monitoring is important until a stable maintenance dose has been determined.

Whenever feasible, oral anticoagulant treatment should be continued after the patient is discharged from the hospital. The use of supplemental therapy in ambulatory patients has been shown to reduce the frequency of recurrent thromboembolic complications.[9] The patient with a first episode of venous thrombosis is treated for a period of 4–6 months. A longer period of therapy may be desirable for the individual who has developed recurrent episodes. Whether alternative prophylaxis with self-injection of low-dose heparin is equally effective is still unresolved.[10, 11]

Major hemorrhage has complicated therapy in about 2% of hospitalized patients, with minor bleeding in approximately 5%.[12] Bleeding is somewhat more frequent in ambulatory patients but is usually minor and manageable solely by adjustment of the dose of oral anticoagulant. The use of vitamin K_1 to reverse the anticoagulant effect is reserved for major episodes of hemorrhage, because patients frequently become more refractory to subsequent administration of anticoagulant. All patients receiving oral anticoagulants should be carefully evaluated for the intake of other drugs which may interact with and influence anticoagulation;[13] no interacting drug should be introduced or withdrawn during oral anticoagulant therapy without careful serial monitoring of changes in prothrombin activity.

Thrombolytic Agents

Since thrombolytic agents of adequate potency have been in clinical use

for a much shorter period of time, definitive cost-benefit data are not yet available. A recent consensus development conference sponsored by the National Institutes of Health has justifiably advocated their more widespread use in patients with major venous thromboembolism of recent origin,[14] but much more information is required regarding the most appropriate agent or combination of agents, dosage, duration of therapy, route of administration, patient selection, and tests for monitoring effectiveness and hemorrhagic tendency.

The 2 products currently approved by the Food and Drug Administration are streptokinase, derived from cultures of β-hemolytic streptococci, and urokinase, extracted from human fetal kidney cell cultures. Streptokinase acts by formation of a plasminogen-streptokinase activator complex while urokinase acts directly to convert plasminogen to the serine protease, plasmin. The proteolytic enzyme, plasmin, produces fibrinolysis and, secondarily, fibrinogenolysis. When these agents are administered IV, fresh thrombi or pulmonary emboli may partially or completely lyse within 12–72 hours; the longer period of treatment has been used more frequently in the treatment of deep venous thrombosis, but the ideal duration of therapy is not yet known.

Streptokinase is usually administered in a loading dose of 250,000 units over 30 minutes followed by an infusion of 100,000 units/hour. Urokinase has been given in a loading dose of 4400 units/kg of body weight followed by hourly infusion of a similar dose. Both agents may produce a pyrogenic or an allergic response; some investigators pretreat patients with hydrocortisone to suppress allergic reactions. Prior to treatment, laboratory tests should include hematocrit, platelet count, prothrombin time, APTT, and TCT; some physicians would include measures of euglobulin lysis and fibrinogen. All of these values should be within normal or acceptable limits before starting therapy. A 2-fold or greater prolongation of TCT is evidence that a fibrinolytic state has been produced, but the magnitude of the prolongation appears to have little or no value in predicting risk of bleeding or extent of thrombus dissolution.[15] If the thrombin time exceeds 5 times normal, the infusion is terminated until a repeat determination reaches this limit. If serious bleeding occurs, thrombolytic therapy should be discontinued and blood loss should be replaced; since the half-life of these agents in the circulation is quite short, the use of ϵ-aminocaproic acid is seldom necessary. When massive bleeding is present, a loading dose of 5 g of ϵ-aminocaproic acid is given IV, followed by 1 g/hour for the next 2–4 hours. To lessen the risk of bleeding during use of these agents, all nonessential invasive procedures, including SC and intramuscular injections, should be avoided and concomitant use of heparin or antiplatelet agents should be prohibited. Two to four hours after termi-

nation of the infusion, clotting studies are repeated and have usually returned to values (TCT less than twice normal) which permit initiation of heparin therapy. Since thrombolytic therapy is adjunctive in nature, it should be followed by treatment with heparin and oral anticoagulants.

Unless very careful patient selection is used, bleeding complications will be more frequent than with anticoagulant therapy. Major contraindications to use of these agents include patients with uncorrected hemostatic defects, cerebrovascular accident or other active intracranial diseases (within 2 months), recent operation or postpartum state or severe trauma (within 10 days), recent needle puncture of major vessels, organs, pleural or peritoneal cavities, or subdural space. Other situations in which thrombolytic therapy should not be utilized except after careful consideration of risk-benefit are severe hypertension, pregnancy, advanced age, ulcerative lesions of the gastrointestinal tract, bacterial endocarditis, major hepatic or renal disease, and recent cardiopulmonary resuscitation.

Since both streptokinase and urokinase are expensive drugs, further studies of cost effectiveness are necessary before definitive statements concerning patient selection can be made. In the recent clinical trials of these agents in the treatment of pulmonary embolism, although more rapid resolution of emboli occurred during the first 5 days of therapy when thrombolytic drugs plus heparin were compared with heparin therapy alone, there was no difference in mortality between the 2 groups of subjects. If mortality alone is considered, thrombolytic therapy may have a significant effect only in patients with hemodynamically unstable, immediately life-endangering, massive pulmonary embolism. Whether there is a clinically important influence of thrombolytic agents upon long-term morbidity from pulmonary embolism is still equivocal. Similarly, although there are some suggestive data to indicate that treatment of iliofemoral venous thrombosis with streptokinase may achieve complete thrombolysis[16] and lessen postphlebitic sequellae,[17] further investigations are required to confirm these findings and to determine whether certain subjects (e.g. those with isolated segmental femoral or iliac veins thrombosis) are more likely to benefit than others. In the interim, in the absence of any of the contraindications listed above, thrombolytic therapy should be considered in patients with angiographically proven major pulmonary embolism and in individuals with venographically documented iliofemoral venous thrombosis.

William W. Coon, M.D.
University of Michigan Medical Center
Department of Surgery
1405 East Ann Street
Ann Arbor, Michigan 48109

References

1. Willis, P.W., III, Coon, W.W.: Pulmonary embolism and infarction, *in* Cardiac Emergencies. Edited by D. T. Mason. Williams and Wilkins Co., Baltimore, 1978, p. 224.
2. Salzman, E.W., Deykin, D., Shapiro, R.M., et al.: Management of heparin therapy: Controlled prospective trial. N. Engl. J. Med., *292:* 1046, 1975.
3. Glazier, R. L., Crowell, E. B.: Randomized prospective trial of continuous versus intermittent heparin therapy. JAMA, *236:* 1365, 1976.
4. Powers, P.J., Cuthbert, D., Hirsh, J.: Thrombocytopenia found uncommonly during heparin therapy. JAMA, *241:* 2396, 1979.
5. Malcolm, I.D., Wigmore, T.A., Steinbrecher, U.P.: Heparin-associated thrombocytopenia: Low frequency in 104 patients treated with heparin of intestinal mucosal origin. Can. Med. Assoc. J., *102:* 1086, 1979.
6. Marciniak, E., Gockerman, J.P.: Heparin-induced decrease in circulating antithrombin III. Lancet, *2:* 581, 1977.
7. Chan, V., Chan, T.K.: Heparin-antithrombin binding. Haemostasis, *8:* 373, 1979.
8. Wessler, S., Gitel, S.N., Bank, H., et al.: An assay of the antithrombotic effect of warfarin: Its correlation with the inhibition of the stasis thrombosis in rabbits. Thromb. Haemostasis, *40:* 486, 1978.
9. Coon, W.W., Willis, P.W., III: Recurrence of venous thromboembolism. Surgery, *73:* 823, 1973.
10. Hull, R., Delmore, T., Genton, E., et al.: Warfarin sodium versus heparin in the long-term treatment of venous thrombosis. N. Engl. J. Med., *301:* 855, 1979.
11. Bynum, L.J., Wilson, J.E., III: Low-dose heparin therapy in the long-term management of venous thromboembolism. Am. J. Med., *67:* 553, 1979.
12. Coon, W.W., Willis, P.W., III: Hemorrhagic complications of anticoagulant therapy. Arch. Intern. Med., *133:* 386, 1974.
13. Coon, W.W.: Use of anticoagulant drugs. Ration. Drug Ther., *13: (10)* 1979.
14. Thrombolytic Therapy in Thrombosis. National Institutes of Health Consensus Development Conference, Vol. 3, No. 1, 1980.
15. Marder, V.J.: The use of thrombolytic agents: Choice of patient, drug administration, laboratory monitoring. Ann. Intern. Med., *90:* 802, 1979.
16. Duckert, F., Müller, G., Nyman, P., et al.: Treatment of deep vein thrombosis with streptokinase. Br. Med. J., *1:* 479. 1975.
17. Johansson, L., Nylander, G., Hedner, U., et al.: Comparison of streptokinase with heparin: Late results in the treatment of deep venous thrombosis. Acta Med. Scand., *206:* 93, 1979.