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Control of Heparin Therapy

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Summary: Heparin therapy in 114 patients was controlled by daily blood tests—the whole blood coagulation time, kaolin-activated partial thromboplastin time of plasma, and plasma heparin assay. Bleeding episodes occurred in 7 out of 92 patients (7.6%) who had normal haemostatic mechanisms before therapy and in 11 out of 22 patients (50%) with defective haemostasis, mostly due to intravascular coagulation or renal failure. The dose of heparin ranged from 20,000 to 60,000 units in each 24-hour period. In some patients bleeding was related to overdosage, but in others the laboratory tests indicated satisfactory or suboptimal dosage at the time of bleeding. Though there were positive correlations between the results of the three tests, these were not close, and no one test was preferable. Hence laboratory control of heparin therapy is unsatisfactory and patients may bleed despite careful control of the dose by all three methods.

Introduction

Heparin is a powerful anticoagulant widely used and of established value in the management of thromboembolic disease. It has also been used recently in the treatment of disseminated intravascular coagulation, microangiopathic haemolytic anaemia, haemolytic-uraemic syndrome, impending renal homograft rejection, and some types of renal failure (Brain *et al.*, 1968; Kincaid-Smith *et al.*, 1968). Haemostasis is often impaired in these latter disorders, most commonly owing to thrombocytopenia or platelet dysfunction, and heparin therapy would be expected to be associated with a considerable risk of bleeding in such patients. The extent of this risk, however, has not been defined but would presumably be related to dosage and to adequacy of laboratory control. Even when heparin is used in the treatment of thromboembolism there are conflicting reports on the incidence of bleeding episodes. Kernohan and Todd (1966) reported 12 bleeding episodes in 82 treatments, Jick *et al.* (1968) 23 episodes in 97 treatments, while O'Sullivan *et al.* (1968), using strict laboratory control of therapy, experienced only four bleeding episodes in 100 treatments; in two of these the patients were being treated concurrently with oral anticoagulants.

Methods available for the control of heparin therapy include the whole-blood coagulation time, kaolin-activated partial thromboplastin time of plasma (Spector and Corn,

1967), and measurement of plasma heparin concentration by protamine titration (Dacie and Lewis, 1968). In this paper the results of these three tests in a group of patients receiving heparin are compared. Since one aim of such tests is to indicate the presence of overdosage, bleeding episodes, when they occurred, were analysed with respect to the laboratory findings at the time bleeding began.

Patients and Methods

Multiple tests were performed on 229 occasions on 87 patients who were receiving heparin by continuous infusion. In addition, therapy was controlled by either the whole-blood coagulation time or the plasma heparin assay in another 27 patients, giving data on 114 patients in all. Most patients were treated by drip infusion, the heparin dose for a 12-hour period being added to 1 litre of saline or dextrose-saline. Some patients were treated by constant infusion pump, the 24-hour dose being added to saline in a syringe preset to administer 2 ml. of fluid per hour. Blood was drawn daily for tests of heparin control and the dose adjusted on the basis of the results obtained. Bleeding episodes have been analysed only if tests were performed on the day concerned.

Tests for Blood Heparin Activity.—Whole-blood coagulation times were estimated by the Lee-White method at 37°C., a portable water bath at the bedside being used. The normal range is four to nine minutes. The kaolin-activated partial thromboplastin time (normal range 30 to 45 seconds) and plasma heparin assay were performed on citrated samples of plasma collected at the same time as the coagulation time test. For the purpose of dose adjustment, a whole-blood coagulation time between 15 and 25 minutes and a plasma heparin concentration ranging from 0.5 to 1.5 units/ml. were considered desirable. No limits were set on the results of the partial thromboplastin time.

Results

Correlation between Laboratory Tests

There were positive correlations between the results of the three tests, but these were not close (Figs. 1-3). The correlation coefficient *r* between the results of whole-blood coagulation time and activated partial thromboplastin time of plasma (Fig. 1) was 0.6009. A whole-blood coagulation time between 15 and 25 minutes was, however, associated with a range of partial thromboplastin times of 50 to more than 300 seconds

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FIG. 1.—Correlation between whole-blood coagulation time and kaolin-activated partial thromboplastin time of plasma. Correlation coefficient $r=0.6009$, $P<10^{-4}$.

FIG. 2.—Correlation between whole-blood coagulation time and plasma heparin concentration. $r=0.6155$, $P<10^{-4}$.

FIG. 3.—Correlation between partial thromboplastin time and plasma heparin concentration. $r=0.6362$, $P<10^{-4}$.

(Fig. 1). Similarly, a partial thromboplastin time between 60 and 100 seconds, considered a satisfactory range by Spector and Corn (1967), was associated with whole-blood coagulation times between 4 and 40 minutes. The correlation coefficient between whole-blood coagulation time and plasma heparin concentration (Fig. 2) was 0.6155. Plasma heparin levels

between 0.5 and 1.5 units per ml., however, were associated with coagulation times between 4.5 and 38 minutes. The correlation coefficient between partial thromboplastin time and plasma heparin concentration was 0.6362 (Fig. 3); again there was a wide scatter of results, plasma heparin levels between 0.5 and 1.5 units per ml. being associated with partial thromboplastin times between 30 and more than 300 seconds.

The correlation between the three tests worsened as the anticoagulant effect became more pronounced. This was not due to greater inaccuracy of the tests at high levels of anticoagulation, since the experimental error of duplicate readings (less than 10% for clotting times and less than 5% for partial thromboplastin times) did not increase with the longer times.

Incidence of Bleeding Complications

Bleeding during heparin therapy was recorded in 18 of the 114 patients, an overall incidence of 15.8%. Twenty-two patients, however, had defective haemostasis at the beginning of heparin therapy, owing to renal failure or disseminated intravascular coagulation with thrombocytopenia; bleeding occurred in half of these patients. Only 7 out of 92 patients (7.6%) with normal haemostasis at the beginning of therapy suffered from bleeding.

Tests for heparin control were performed on 10 of the 18 patients on the day of bleeding. Brief clinical details and the laboratory results are shown in the Table. In seven patients (Cases 1-7) there were complicating factors which might have predisposed to bleeding. The dose of heparin when bleeding occurred ranged from 20,000 to 60,000 units per day. In four patients (Cases 1, 2, 6, and 9) the whole-blood coagulation time was less than the desired range of 15 to 25 minutes. In two of these heparin could not be detected in the plasma at the time of bleeding, while in the other two the plasma heparin concentration was in the desired range (0.5 to 1.5 units/ml.). In four patients (Cases 3, 5, 7, and 10) the whole-blood coagulation time was undesirably long at the time of bleeding. In two of these the plasma heparin concentration was also greater than 1.5 units/ml. According to our criteria for laboratory control four patients were underdosed and four were overdosed at the time of bleeding.

There were two deaths partially attributable to heparin in the whole series of 114 patients. One patient (Case 3) died from intracerebral haemorrhage, but she was suffering from renal failure complicating polyarteritis nodosa. The other fatality occurred in a 71-year-old woman with polycythaemia vera and pulmonary embolism who developed a retroperitoneal haemorrhage on heparin therapy.

Discussion

Heparin interferes with blood coagulation in a complex manner. A well-recognized action is the inhibition of the thrombin-fibrinogen reaction, resulting in a prolonged thrombin clotting time of plasma. In addition, heparin potentiates the neutralization of activated factor X by its natural plasma inhibitor and so retards the intrinsic blood coagulation system (Yin and Wessler, 1970). A further effect on intrinsic coagulation is produced by thrombin neutralization, since thrombin catalyses the activation of factor IX by activated factor XI (Shanberge and Fukui, 1967). The whole-blood coagulation time and the plasma partial thromboplastin time are essentially tests of the intrinsic coagulation system and do not measure antithrombin activity, which is the basis of the plasma heparin assay. Nevertheless, it is disturbing to find such poor correlation between the three sets of results. It is the custom to control heparin dosage by the whole-blood coagulation time, but this test has practical disadvantages, being time-consuming and requiring the presence of a technician

Details of 10 Patients Who Bled on Heparin Therapy

Case No.	Age	Sex	Condition	Heparin Dose (units $\times 10^3$ /day)	Type of Bleeding	Whole-blood Coag. Time (min.)	Partial Thromboplastin Time (sec.)	Plasma Heparin (u./ml.)	Other Findings Contributing to Bleeding
1	49	F	Deep-vein thrombosis	30	Retroperitoneal haemorrhage	5	45	Nil	Reticulum-cell sarcoma
2	48	M	Polyarteritis nodosa	50	Haemoptysis. Haematoma of abdominal wall	11	60	1.0	Blood urea 386 mg./100 ml.
3	44	F	Polyarteritis nodosa	24	Intracerebral haemorrhage	37	156	1.5	Blood urea 320 mg./100 ml.
4	60	F	Disseminated intravascular coagulation; cause unknown	40	Haemoptysis. Vaginal bleeding	16	55	0.25	Platelets 54,000/mm. ³
5	52	M	Septicaemia, acute renal failure. Disseminated intravascular coagulation	40	Epistaxis	111	Not done	1.5	Blood urea 180 mg./100 ml. Platelets 57,000/mm. ³
6	19	F	Septicaemia, acute renal failure. Disseminated intravascular coagulation	40	Bleeding from site of peritoneal dialysis. Bleeding about venepuncture sites	9	35	Nil	Blood urea 130 mg./100 ml. Platelets 42,000/mm. ³
7	23	F	Rejection of renal homograft	20	Bleeding from renal biopsy site and venepuncture sites	41	153	2.0	Blood urea 340 mg./100 ml.
8	65	M	Deep-vein thrombosis. Pulmonary embolism	60	Haematemesis and melaena	25	90	2.0	None
9	59	F	Deep-vein thrombosis. Pulmonary embolism	60	Haematuria	12	Not done	0.5	None
10	59	M	Deep-vein thrombosis. Ligation of superficial femoral vein	40	Bleeding from operation site	> 90	> 600	3.5	None

with a portable water-bath at the bedside. The kaolin-activated partial thromboplastin time is performed in the laboratory on plasma samples, is rapid and relatively simple to carry out, and is more sensitive than the whole-blood coagulation time in detecting defects in the intrinsic coagulation mechanism. While we found a positive correlation between the results of these two tests, there was a wide scatter of individual readings suggesting that the two tests were not comparable in their sensitivity to the defect produced by heparin. The experimental error involved in these tests was unlikely to have been a major factor in the poor correlation.

An analysis of the bleeding episodes indicates the difficulty of maintaining the whole-blood coagulation time and plasma heparin concentration between defined limits despite daily measurements and adjustments of dosage. An important technical reason may be fluctuations in the drip flow rate, and clotting-time fluctuations are less if heparin is administered by a constant infusion pump (Handley, 1967). Another factor is the altering sensitivity of the individual patient to heparin during therapy (Gurewich *et al.*, 1967; Morris and Balk, 1967; O'Sullivan *et al.*, 1968), patients commonly being more resistant immediately after a thrombotic episode. This early resistance could be due to release of antiheparin activity (platelet factor 4) from platelets involved in the thrombotic process (Youssef and Barkhan, 1968) or to circulating activated coagulation material (Dewhurst and Poller, 1965). O'Sullivan *et al.* (1968) found that only 42% of patients did not require a significant change in dose during therapy; the dose was increased in 33% and decreased in 25%. Our patients suffered bleeding at doses ranging from 20,000 to 60,000 units of heparin per day. Patients with renal failure or thrombocytopenia are especially at risk from bleeding during heparin therapy (see Table). Though we observed instances where bleeding was clearly related to overdosage, in others the laboratory tests indicated what we had considered to be satisfactory or suboptimal dosage at the time of bleeding.

The control of heparin therapy poses considerable problems. When a powerful anticoagulant is used to produce a derangement of haemostasis a risk of haemorrhage is inevitable, and the intensity of this risk would be expected to be related to the degree of anticoagulation achieved. The aim of therapy is to administer a dose of heparin sufficient to be effective, yet low enough to carry an acceptable risk of haemorrhage. Though few would doubt the effectiveness of heparin in the treatment of thromboembolic disease, there is no uniformity of opinion concerning the optimal dose or its laboratory control and the method of administration (Deykin, 1969). It was recommended by Thomas (1965) that the minimum dose of heparin for the treatment of pulmonary

embolism should be that which maintains the whole-blood coagulation time in excess of twice the control value, since this level of anticoagulation was necessary to prevent formation or propagation of experimental venous thrombi in dogs (Carey and Williams, 1960; Gurewich and Thomas, 1965). There is no clinical evidence available to indicate the degree of prolongation of the coagulation time which is necessary to prevent formation or propagation of venous thrombi in man. The therapeutic range of 15 to 25 minutes adopted in the present study seemed to be reasonable and to conform with usual practice.

The results of the other tests do not indicate that either the plasma partial thromboplastin time or the plasma heparin assay, though technically more convenient, is any more reliable than the clotting-time method for the control of therapy. Despite the fact that some patients bled when the clotting time indicated satisfactory or suboptimal dosage, we believe that the risk of haemorrhage can be minimized by laboratory control, but are unable to recommend any one test as being preferable to the other two.

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