Heparin therapy: A simpler test of control

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SYNOPSIS A bedside test of heparin activity (whole blood activated partial thromboplastin time) was assessed during clinical control of anticoagulation. It correlated closely ($r = 0.94$) with the whole blood clotting time but had a number of advantages.

Experimental evidence has suggested that the optimum dose of heparin is that which maintains a patient's whole blood clotting time over twice the normal time (Carey and Williams, 1960; Gurewich and Thomas, 1965). This level of anticoagulation can be accurately maintained by using an intravenous infusion pump (Handley, 1967), and can be shown to be therapeutically effective, at least as far as prophylaxis against deep vein thrombosis is concerned (Handley, Emerson, and Fleming, 1972). However, the dose of heparin required to produce a given anticoagulant effect in an individual patient varies widely (O'Sullivan, Hirsch, McCarthy, and De Gruchy, 1968), and there is thus a need for some form of haematological control. The standard test used is the whole blood clotting time (WBCT) (Lee and White, 1913). This is time-consuming and very dependent both upon standardization of technique and on cleanliness of clotting tubes. A variety of other coagulation tests have been shown to correlate reasonably well with the WBCT, including the partial thromboplastin time (MacAulay, Frisch, and Klionsky, 1968), activated partial thromboplastin time (Pitney, Pettit, and Armstrong, 1970), and plasma heparin assay (Pitney *et al.*, 1970). None would appear to be better than the WBCT and all require to be performed in the laboratory. Under experimental conditions the whole blood activated partial thromboplastin time ('activated clotting time' or AcCT) is a bedside test which seems to correlate well with the WBCT, and to have certain advantages (Blakely, 1969; Estes, 1970). A slightly modified version of this test was compared with the WBCT during clinical control of heparin therapy.

Subjects and Methods

The subjects were 20 patients receiving heparin by

continuous intravenous infusion for the treatment of deep vein thrombosis or pulmonary embolism or as prophylaxis against thromboembolism following myocardial infarction. The dose was initially 20 000 units 12-hourly, without a 'loading dose', but was adjusted as necessary to produce a WBCT between two and four times normal. The whole blood clotting time and AcCT were measured simultaneously as often as necessary until this degree of anticoagulation was achieved. Some blood samples were deliberately taken within a short time of the start of the heparin in order to obtain pairs of tests at the lower end of the therapeutic range. Alterations in heparin dosage, however, were only made on the results of tests performed at least six hours after the start of therapy. Similar pairs of tests were also performed on blood from 30 normal control subjects.

Whole Blood Clotting Time

One ml of blood was carefully added immediately after venepuncture to each of four glass tubes (9 mm $\times$ 75 mm) which had been washed in acid and alcohol and dried in an oven. The tubes were incubated in a water bath at 37°C and all four tilted gently every 30 seconds until a clot formed. The mean of the four clotting times was recorded to the nearest 15 seconds.

Activated Clotting Time

Kaolin suspension, 0.1 ml, in Tris buffer (0.5 mg/100 ml at pH 7.4) and 0.1 ml of partial thromboplastin (Thrombafax, Ortho) were added to each of two disposable plastic tubes (8 mm $\times$ 65 mm) in a water bath at 37°C. After leaving time for the reagents to reach 37°C, 0.5 ml of freshly drawn blood was added to each tube which was then closed with a plastic stopper. Both tubes were inverted every 10 seconds until the blood clotted. The mean of the two clotting times was recorded to the nearest five seconds.

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Results

The WBCT and AcCT were measured in 30 control subjects. The mean times obtained were WBCT 4.2 minutes (range 3.5-5.5 minutes; SD, 0.48) and AcCT 68.5 seconds (range 50-90 seconds; SD, 7.0).

The whole blood clotting time and AcCT were measured simultaneously on 38 samples of blood from 20 patients receiving heparin. The results obtained are shown in the figure. The regression line

Fig Comparison of whole blood clotting time and 'activated clotting time'. Correlation coefficient $r = 0.94$. Results within the shaded portion are considered to be below the minimum therapeutic requirement, but are included to demonstrate the linear correlation at these levels of anticoagulation.

is drawn; the correlation coefficient $r = 0.94$. The minimum acceptable degree of anticoagulation was a WBCT of 10.5 minutes. This represents twice the upper limit of normal (mean + 2 SD). Sixteen estimations gave results below this level but 12 of these were on samples of blood drawn soon after the start of heparin. The remaining four samples were from patients who had received more than six hours of therapy. In these cases the dose of heparin was increased, further clotting times being measured until the degree of anticoagulation was satisfactory. All pairs of WBCT and AcCT are shown in the figure to demonstrate that the relationship between the two tests remains linear below and throughout the therapeutic range.

Some AcCT tests were performed additionally at room temperature. Very poor reproducibility was obtained between the two tubes and the correlation

with WBCT was also very poor. This is similar to the findings of Ray and Harper (1971).

Discussion

The AcCT has been shown to correlate well with the WBCT in the control of heparin therapy. It will be seen that doubling the AcCT is not the same as doubling the WBCT. Since published recommendations for optimum heparin dosage have been based upon the WBCT it would seem reasonable to use this test as the standard. The corresponding range for AcCT can then be found from the figure. Assuming that one wishes to prolong the WBCT to between two and four times the upper limit of normal, the therapeutic ranges are: WBCT 10.5-20 minutes; AcCT 130-200 seconds.

The AcCT had a number of advantages over the WBCT: (a) the endpoint of clotting was much clearer. (b) The time taken to perform the test was much shorter. (c) Disposable plastic tubes gave similar results and were more convenient to use than glass tubes. (d) The technique was easily taught to medical and nursing staff and reproducible results were obtained more readily than with the WBCT.

There were a number of minor disadvantages which included the need for a water bath (also required for most other coagulation tests), the need to keep the partial thromboplastin in a refrigerator, and the need to pipette accurately quantities of 0.1 ml, particularly when the test was performed by ward staff. This last difficulty was overcome by providing stoppered disposable plastic tubes, each containing the required amounts of reagents and marked with a line to which blood should be added. These were kept in ward refrigerators and transferred to the water bath shortly before use.

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