The Subcutaneous Use of Heparin

A Summary of Observations

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Because there is a definite need for an anticoagulant which need not be injected intravenously, and because of our conviction that dicumarol prophylaxis and therapy are at present unsafe and unpredictable, 1 an investigation of various heparin solutions and suspensions was undertaken with regard to their injectability and efficacy through a deep subcutaneous route. When the site of so-called intramuscular injections—as given by the nursing staff—is examined by biopsy, it is often found to be the deep subcutaneous tissue. The samples tested were 200 mg. of heparin in gelatin, 2 with and without vasoconstrictors, 400 mg. of heparin in gelatin with and without vasoconstrictors, 200 mg. of heparin in gelatin with, and 200 mg. of depo-heparin without vasoconstrictors and 10 per cent heparin in aqueous solution in doses of 100 and 200 mg.

General Considerations

While in the case of penicillin the infecting organism is the dominating factor determining penicillin resistance or penicillin sensitivity, in the case of heparin, there is a multiplicity of factors influencing its action. These have been summarized in table 1. In addition, there may be a daily change in heparin requirement, and there also seems to be a cumulative action, or possibly a phenomenon of storage. 3 All this indicates the difficulty in prescribing set dosages, and the necessity of utilizing a test dose of heparin (10 mg. in 1 cc. solution given intravenously) before heparin therapy is started. 4 The effect of this dose on the individual is tested by capillary coagulation times, determined before and 10 minutes after the injection. Such tests reveal nonreactors, hyporeactors, mean reactors and hyperreactors. Of 97 normal individuals tested a few years ago, 40 were hyporeactors, 31 were hyperreactors and 20 were mean reactors. 1 In 250 patients there was a much higher percentage of hyporeactors, and nonreactors appeared. The guiding influence of such a test dose on prophylactic and therapeutic dosage is obvious.

Heparin activity can be controlled by coagulation times, and for years we have employed capillary coagulation times for this purpose because (1) this is a simple bedside test, and can be performed by technicians, internes, nurses and even patients; (2) repeated venipunctures in patients under heparin therapy produce hematomata; (3) coagulation times with the one tube Lee-White method may be prolonged from 40 to 60 minutes during therapy with heparin, producing a time consuming procedure; (4) three and five tube Lee-White coagulation times may start with a 25 to 30

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1 This cartridge of Depo-heparin sodium, 200 mg., with vasoconstrictors contains: heparin sodium (20,000 units), 200 mg.; epinephrine hydrochloride 1 mg.; ephedrine hydrochloride, 10 mg.; gelatin, 180 mg.; dextrose, 80 mg. Preserved with sodium ethyl mercuri thiosalicylate 1:10,000.
minute normal coagulation time\(^4\) and silicone-coated tubes may exhibit a 60 to 70 minute normal coagulation time,\(^2\) indicating that all these methods are pure artefacts and that the blood surrounded by a nonwettable endothelial lining does not clot anyway.

For these reasons, capillary coagulation times are advocated, not with the idea of studying the patient’s clotting mechanism, but merely to follow and control the administration of heparin. Heparin can of course be titrated in whole blood and in plasma with protamine sulfate, but in our opinion this can never become a satisfactory bedside test for the control of heparin administration. Heparin tolerance can also be tested in vitro,\(^4\) although as pointed out by Best and Jaques\(^5\) the clotting time produced with moderate doses of heparin in vivo is considerably greater than that obtained on mixing the same quantity of heparin with the blood in the test tube. The heparin tolerance in the circulating blood measures the state of the clotting mechanism, a dynamic equilibrium of coagulant and anticoagulant factors, and in addition is influenced by excretion, storage and enzymic degradation.\(^6\) This is the reason why single large intravenous doses are wasteful, and a moderately elevated plateau-type of clotting curve is desirable.

The addition of minute amounts of heparin (1 to 4 gamma) to a cubic centimeter of blood in vitro reacts with a number of enzymes, cofactors, profactors and accelerators,\(^7\) the sum total of which inhibit or facilitate the action of heparin, but it is most useful in sensitizing the ordinary Lee-White method of venous coagulation time so that small amounts of additional heparin as used in subcutaneous therapy may be detected by lengthening of the clotting time. Our experience with the recently published method of Rosenthal\(^8\) has been most satisfactory, and has gradually led us to adopt the principle that, for prophylactic purposes, the maintenance of a sensitized clotting time at the upper limit of normal is protective. This means the use of far smaller quantities of heparin than have been advocated in the past, amounting for the adult of average weight to 200 mg. of heparin every 48 hours in a retarding medium such as gelatin. The normal sensitized clotting time varies between 20 and 30 minutes, using 4 gamma as a sensitizer. Figures below or above these indicate hypocoagulability or hypercoagulability of the blood. Elsewhere we have reported on the clinical value of such a sensitized clotting time.\(^9\)

**Methods of Study**

The patient’s age, sex, diagnosis and other conditions known to influence the response to heparin were noted. A heparin tolerance test was run on each individual before the administration of heparin. A coagulation time was determined before and every two hours after the administration of heparin until the pre-injection level of coagulation time was reached. Often capillary coagulation times were determined more frequently until the peak was reached. Untoward effects, such as pain or hematoma at the site of injection, or bleeding elsewhere, were noted.

**Observations**

(1) 200 Mg. of Depo-Heparin without Vasocostrictors. Figure 1 shows a control of this drug by venous coagulation times. Note that the effect is over in about 12 hours and that the peaks are so high as to make the venous coagulation times impractical. Figure 2 shows the control by capillary coagulation times. Thus, case 6 in figure 2 shows a poor response. This patient, Esther O., a heavy set woman with chronic thrombophlebitic edema, showed marked heparin resistance following operation. In contrast, case 3, a young boy who had just recovered from a massive acute thrombopha-
bitis, showed a good response. The same heparin sensitivity is exhibited by case 4, figure 1, a patient with Buerger's disease in a state of remission.

(2) 200 Mg. of Depo-Heparin with Vasocostrictors. Figure 3 shows the control with venous coagulation times, whereas figure 4 illustrates the control by capillary coagulation times. The highest response in figure 3 is shown by case 10, Bernice O’F., a 30 year old woman with a postphlebitic syndrome. The peak and duration of effect is quite variable. Case 1 of figure 4 is Mary S., a young girl with a congenital vascular anomaly but no thromboembolic disease, who showed a peak of 11 minutes and duration of effect to 30 hours. Case 4 on the other hand is an arteriosclerotic individual of 56, with extensive arterial and venous thrombosis who showed little therapeutic effect; even less did case 6, Charlotte K., who exhibited a postoperative infection. The average duration of effect, which varied from 9 hours to 30 hours, was 22 hours.

Fig. 1. The effect of 200 mg. of heparin-gelatin without vasocostrictors on venous coagulation time. Note the high peaks, the steep curves, and the relatively short duration.

Fig. 2. The effect of 200 mg. of heparin-gelatin without vasocostrictors on capillary coagulation time. Note the marked variation in response. Case 3 exhibits an exaggerated response in a young boy during the stage of recovery from an acute thrombophlebitis. Case 6 is in a stage of postoperative heparin-resistance.

(3) 400 Mg. of Depo-Heparin without Vasocostrictors. Figure 5 illustrates the effect of this dose, measured by capillary coagulation time, and indicates again extreme variability. The high curve with a peak of 32 minutes and a duration of effect up to 38 hours belongs to
Wm. P., a thin, undernourished individual who received with this dose (3.5 mg. of heparin per pound of body weight) an overdose resulting in a large hematoma at the site of injection. On the other hand, curve 3 belongs to Esther O., the same individual who showed poor response to heparin in Figure 3 to 200 mg. of depo-heparin with vasoconstrictors. Her curve dropped to the preinjection level in 12 hours. The duration of effect varied from 19 to 35 hours, with an average of 31 hours.

(4) 400 Mg. of Depo-Heparin, 200 Mg. with, and 200 Mg. without, Vasoconstrictors. Figure 6 illustrates the control with capillary coagulation times. These curves are more of a plateau type, show fewer peaks and last from 16 to 32 hours, with an average of 25 hours. Note the almost complete lack of response of case 8, Henry H., an obese individual with multiple, massive venous and arterial thromboses.

(5) 400 Mg. of Depo-Heparin with Vasoconstrictors. Figure 7 shows the capillary control. The duration of effect varied from 13 to 48 hours, an average of 27 hours. Noteworthy among the poor responses in the individual
The effect of 400 mg. of heparin in gelatin with full dose of vasoconstrictors. Capillary coagulation times were used. These are flat curves. Note that in case 2 the effect lasted for 36 hours; in case 5 for 19 hours. Both patients weighed the same, but case 5 had an acute, case 2 a chronic thrombophlebitic edema.

Fig. 7. The effect of 400 mg. of heparin in gelatin with full dose of vasoconstrictors. Capillary coagulation times were used. These are flat curves. Note that in case 2 the effect lasted for 36 hours; in case 5 for 19 hours. Both patients weighed the same, but case 5 had an acute, case 2 a chronic thrombophlebitic edema.

Fig. 8. The effect of 200 mg. of heparin in 10 per cent aqueous solution, given intramuscularly. Capillary coagulation times were used. Note the difference in response between case 2 and case 6. The former received protamine for a severe hemorrhage in an abdominal incision. Case 3 had a subsiding deep thrombophlebitis, with a capillary coagulation time of 38 minutes, at 6 hours, but showed no bleeding.

Fig. 9. The effect of intravenous protamine sulfate on the action of heparin. In the left row of curves (V.S.) 50 mg. of heparin were given intravenously, alone; a second time at the peak of response protamine was given; a third time heparin and protamine were given simultaneously. The dose of protamine was one half that of heparin. Note a dampening, but not a neutralizing effect. In the middle row and in the third row, a 1.5 to 1 ratio of protamine to heparin was used. Note that in patients F. L. and S. W., protamine, given at the peak, promptly restored the clotting time to normal; given simultaneously, it completely neutralized the effect of heparin, which showed a good effect in both patients when given alone.

ministered to patients weighing around 120 pounds, this dosage was administered to a few patients. Even this dose resulted in a large postoperative hematoma in Vesta W., who received 1.71 mg. of heparin per pound of body weight. This case will be discussed under the heading of untoward reactions.

(7) 200 Mg. of Heparin in 10 Per Cent Aque-
ous Solution. There is again a tremendous variation in the effect of this injection. Figure 8 shows the capillary control with high peaks and a duration varying from 7 to 19.5 hours. One case in this group developed a severe hemorrhage. This patient, case 2 of Figure 8, will be discussed in detail. Note the poor response of case 6, J. B., a 44 year old vascular sclerotic, whose capillary coagulation times hardly show a rise.

The Neutralization of Heparin by Protamine Sulfate

Various doses of protamine sulfate were given intravenously to neutralize the action of heparin (fig. 9). While a 1:1 ratio of protamine to heparin definitely dampens the effect of heparin, a complete suppression of the heparin effect on capillary coagulation time is obtained by a 1.5:1 ratio. Thus 75 mg. of protamine sulfate given simultaneously (but not in the same syringe) with 50 mg. of heparin, has led to the flattening of clotting curves.

When protamine sulfate is given at the height of the clotting curve, within 10 minutes there is a steep fall of the clotting time to a lower level.

Here again a 1.5:1 ratio (i.e. 75 mg. of protamine to 50 mg. of heparin) seems the most effective, but smaller doses, such as a 0.5:1 ratio, are partially effective. (fig. 9).

So far, there have been no untoward reactions following the intravenous use of protamine; when given into muscle there is severe burning for 24 hours, but a noticeable antiheparin effect. We do not advise the latter method of administration unless it can be made more painless, possibly with procaine as in the case of aminophylline.

The duration of the effect of intravenous protamine is approximately four hours. Heparin response up to four hours is abolished or dampened. In case of continuing hemorrhage after administration of heparin, protamine injections must be repeated.

Discussion

With increasing experience we have developed certain guiding principles which of course may have to be modified in the light of further observations. In addition to the factors enumerated in table 1, weight is an important factor in determining heparin response. This is illustrated by patient Wm. P., who received preoperatively 400 mg. of Depo-heparin without vasoconstrictors, resulting in a capillary coagulation time of 32 minutes with a duration of effect to 3 hours, and a large hematoma at the site of injection. The amount he received was equivalent to 3.5 mg. per pound of body weight; in our opinion 2 mg. per pound is sufficient as a preoperative or therapeutic dose. Postoperatively, even the 2 mg. per pound weight dose may be too much, as shown by the case of Vesta W., who received 300 mg. of Depo-heparin (1.71 mg. per pound of body weight) and developed a huge hematoma in the incision of a lumbar sympathectomy. This patient had no thrombosis at the time, but had had this condition in the past. In postoperative prophylaxis 1 mg. of heparin per pound of body weight is a safer daily dose.

This matter raises the question of the advisability of giving large doses of heparin intramuscularly the absorption of which is not under any further control than that given by the gelatin-dextrose menstruum and the vasoconstrictor. However, even with 200 mg. given in 10 per cent aqueous solution, we have observed a severe hemorrhage from an unsuspected cervical erosion in Viola M., who required several transfusions to restore her blood count.

In addition, heparin seems to have a cumulative effect, because a patient whose coagulation time has returned to normal may respond the second and third time with a far longer coagulation time or even with hemorrhage. There are several possible explanations for this which we plan to investigate in the future. Suffice it to say here that, once the patient has received a large dose of heparin, the heparin requirement diminishes, and the return of the capillary coagulation time to a normal level does not mirror the increased sensitivity. Increased heparin sensitivity may be due to several factors, some of which are listed in table 1. From the standpoint of avoiding hemorrhages after heparin administration the following points need emphasis: (1) Small amounts
of heparin remain in the blood stream, although only a single dose of heparin is given for a longer time than venous or capillary coagulation times can detect them. They are demonstrable, however, with a heparin clotting time or heparin titration.* (2) After certain shocklike states, including coronary thrombosis, pulmonary embolism and massive peripheral thrombosis, anticoagulant substances appear in the blood, and they may manifest themselves by increased reactivity to heparin (case 10 of figure 3, and cases 3 and 9 of figure 2). We have again and again seen astonishing responses to heparin after the 10 mg. test dose in patients who were recovering from or had just suffered an acute thrombosis. In such patients

This brings us to the important question: what is the desirable range of capillary coagulation time, a range which is both safe and protective against thrombosis or extension of thrombosis? Our experience, extending over 12 years, indicates that for therapeutic purposes a range between 8 and 12 minutes is effective. There is no need to reach peaks of 20 to 30 minutes. This is uneconomical because so much more of the drug will be excreted through the kidney. Therefore, the plateau type of curve is preferable. The heparin-gelatin emulsion is sometimes painful. While it is a definite improvement over the Pitkin menstruum, our records indicate a 15 per cent incidence of pain of which patients spontaneously complain, some of course more bitterly than others.

Conclusions

A study of the graphs presented indicates that the variability of the patient's response to heparin is great. The value of mass statistics, transferred to punch cards and analyzed for statistical significance, is not questioned; but they will not substitute for a close clinical observation of each patient receiving anticoagulants. The balance of coagulant and anticoagulant factors is delicate and seems to swing spontaneously; the administration of an anticoagulant markedly influences this balance.

Regarding dosage schedules, the following tentative schedule has been followed: a priming dose of intravenous heparin (30 to 50 mg.) is followed by the deep subcutaneous injection of heparin in gelatin. The initial priming dose will raise the capillary coagulation time to 8 to 12 minutes and this should be maintained with the average daily dose of 2 mg., with vasoconstrictors, per pound of body weight. This dose refers to the treatment of acute thrombotic episodes and must be kept up for 14 days. Shorter periods of administration will give rise to the recurrence or flare-up of the thrombosis, when heparin is discontinued. This statement refers to surgical patients; after coronary thrombosis, four weeks seems to be a safer period.

One mg. per pound of body weight is a good average prophylactic daily dose. In the presence

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* Unpublished Data.
of an open lesion, or of a recent surgical incision, this dose must never be exceeded, but may even be split by giving it every second day.

Control of the clotting mechanism is sufficiently safe if a capillary coagulation time is determined once a day, usually in the morning, with the heparin administered at noon-time. When a sensitized clotting time is used, this too can be run once a day and should be kept at the upper limit of normal. Such a control leads to smaller prophylactic doses than have been employed in the past.9

Aside from occasional sensitization to heparin, the only complication of heparin administration is hemorrhage. The following precautions are useful in minimizing this untoward reaction: (1) heparin should be administered according to body weight; (2) following trauma, operation or acute vascular accidents, natural anticoagulants may potentiate the effect of heparin; (3) protamine sulfate should always be on hand and its injection repeated every four hours until hemorrhage stops; (4) hemorrhage continuing in spite of administration of protamine is a rare self-perpetuating mechanism uninfluenced by neutralization of heparin which must be combated by blood transfusions.

SUMMARY

An emulsion of heparin in gelatin, given with a daily control of capillary coagulation times, is a simple efficient anticoagulant therapy. The great variability of response to heparin makes set schedules of dosage impossible. The therapeutic dose should always be double the prophylactic dose; in the case of an acute thromboembolic episode, the administration of heparin should be maintained for two weeks. The determination of heparin tolerance gives a good insight into the state of the clotting mechanism; it can be done in vivo or in vitro.

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