HEPARIN IN INTRAVENOUS INFUSIONS, INCLUDING PENICILLIN THERAPY

BY

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The general, if not the only, anticoagulant used in blood transfusions in this country and in the United States is sodium citrate (0.3 g. per 100 c.cm. of blood). It has proved very satisfactory. It is cheap, and has, it is believed, no deleterious effects. It is not here proposed that heparin should be substituted for sodium citrate, as has been advocated by Hedenius (1937), who administered enough intravenous heparin to give the donor's blood a coagulation time of about 30 minutes: he has used this method hundreds of times with complete success. Rather it is suggested that a very small amount of heparin be employed in addition to the citrate added to blood, or to an infusion of crystalloid solution if this is preferred.

Although there is no essential difficulty in administering either a transfusion of blood (fresh or stored), plasma, serum, or an infusion of crystalloid solution, it sometimes happens that the infused substance fails to run smoothly through the apparatus long enough to give the amount intended. This is generally due either to spasm or to a thrombosis of the recipient's vein. Spasm is seen particularly after dissection of the internal saphenous vein at the ankle, and can be relieved by placing hot-water bottles along the course of the vein; it is then often surprising how, in a few moments, the blood or solution will begin to run freely. We have all met with the patient who has had several transfusions and who, again requiring one, presents no suitable vein that has not been "used" and thrombosed. It is important that a vein should not be obliterated by a transfusion, and it should be possible to use the same vein an indefinite number of times. It generally is; it sometimes is not.

Why is it that sometimes everything works smoothly and there is no residual thrombosis, and at other times thrombosis occurs and the flow stops? The condition is generally due to a thrombotic process starting, presumably, at the site of venepuncture, or to an irritating solution being infused, such as is unfortunately common in intravenous penicillin therapy.

Prevention of Thrombosis

To counteract the incidence of thrombosis in the recipient's vein it is suggested that heparin, in an amount equivalent to 1 Toronto unit per c.cm., be added to the fluid to be introduced. G. Murray (1940) reported on the use of continuous intravenous heparin in over 400 cases without a single case of thrombosis at the site of venepuncture, even though in some instances the needle was left *in situ* for two weeks and though, as he was deliberately prolonging the coagulation time of the recipient's blood, he was using a concentration considerably greater than that suggested here. It may be argued that in a transfusion on account of haemorrhage, or in a transfusion being given during or immediately after an operation, the coagulation time of the recipient's blood is liable to be prolonged. Hedenius has shown that there is a threshold for heparin in the blood below which no alteration in the coagulation time is apparent. This threshold is 0.25 mg. per kilogramme of body weight. In a patient of 8 st. this would amount to 14 mg. of heparin, and in a patient of 10 st. to between 17 and 18 mg. Now, 1 Toronto unit of heparin contains 0.01 mg. of the substance; therefore a litre of blood or crystalloid solution heparinized with 1 unit per c.cm. would contain 10 mg. It will be seen that to reach the threshold it would be necessary to infuse $1\frac{1}{2}$ litres in an 8-st. patient. As the amount of heparin contained in this $1\frac{1}{2}$ litres is destroyed hourly by the body, and as it is very improbable that there would ever be an indication to carry on an infusion at the rate of $1\frac{1}{2}$ litres an hour, it is concluded that the threshold is not reached, and therefore that the coagulation time of the recipient is not affected. This is borne out by the observation made in a few cases.

It might be said that there may be toxic effects of the heparin *per se* and that harm may result. Experimentally, Howell and McDonald (1930), in dogs, have been unable to show any change

in the red and white counts or in the platelets, even where the animal's blood has been rendered incoagulable; and G. D. W. Murray (1940) has given to patients as much as 600,000 units over a period of 40 days without ill effect. Nor have anaphylactic phenomena been encountered where heparinization has been repeated.

We have recently used heparin in all infusions of blood (fresh or stored), plasma, and solutions of crystalloids. The heparin is added to the infusing fluid by injecting it through the cork of the bottle by means of a hypodermic syringe. The amount used has been 1 unit per c.cm. of fluid—equivalent to 1 c.cm. of heparin B.D.H. per litre. The infusion is then carried on in the usual way. We have not had to dissect a vein in this series, and this step should only very rarely be necessary.

Between 50 and 60 cases have received heparinized intravenous therapy, and most varieties of shock, haemorrhage, prolonged sepsis, and anaemic states have been included in this series. There has been no tendency to a recurrence of haemorrhage, and in post-operative cases we have seen no evidence of bruising or haemorrhage in the area of the operation scar. In 8 cases the coagulation time was estimated before infusion and immediately afterwards. In no case was there any significant alteration, the maximum rise in coagulation time being 30 seconds and the maximum fall in value 20 seconds, these variations in the value clearly being within the limits of the margins of error of the test. There has been no evidence of toxic or deleterious effects as a result of the heparin.

Use of Heparin with Penicillin

It is suggested that heparin should be of value in preventing the thrombosis and phlebitis which are frequently seen when penicillin is given by intravenous drip. Penicillin, or at least the impure solution of penicillin available at present, irritates the endothelium of veins, causing a chemical phlebitis and a subsequent thrombosis. However, G. D. W. Murray (1940) has found experimentally that the incidence of phlebitis and thrombosis caused by the intravenous injection of sodium ricinoleate—a powerful intravenous irritant—can be reduced from 90% in controls to less than 20% in heparinized animals. According to Surg. Cmdr. C. A. Green (personal communication), penicillin is not destroyed or affected by heparin. We have in several cases employed heparin with penicillin to try to prevent thrombosis or thrombophlebitis. At first we used 1 unit of heparin per c.cm. of penicillin solution, and in five cases the full amount of penicillin was given without thrombosis, but in one the drip blocked after four and a half days. In a second batch of penicillin 1 unit of heparin per c.cm. did not suffice to prevent thrombosis, so 3 units per c.cm. were used. With this dosage it has been possible to give the required amount of penicillin without accident. At the rate of penicillin drip which we are using—i.e., 35 drops a minute—it would not seem possible to administer enough heparin to affect the clotting time.

Conclusion

Apart from difficulty with the penicillin cases, infusion has been conducted with noticeable ease in every case except one. This patient was receiving fresh heparinized blood for a secondary anaemia and toxic state following prolonged suppuration. In this instance the needle was not inserted fairly into the vein and there was leakage into the perivenous tissues. After the needle was inserted into the other arm all went well, and an infusion of 4 pints of blood was successfully concluded. The original vein did not thrombose.

In no case has thrombosis of the recipient vein been seen, nor has there been any bruising of the tissues around the site of puncture. Objection to the use of heparin in infusions has been raised on the question of cost. At present heparin B.D.H. costs 8s. 6d. for 5 c.cm., which contains 5,000 units—enough to heparinize effectively 5 litres of blood, plasma, or other fluid. A cost of approximately 1s. 8d. per litre cannot, therefore, be regarded as excessive when the advantages of the method are considered.

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