drug interaction was noted at the time of the interview in only three patients but as they were seen on only one occasion many more may have had varying blood pressure levels.

These studies show that in patients in the community on long-term anticoagulant or antihypertensive drugs particular care is required when additional drug therapy is prescribed and when the patient is advised about self-medication. A record of current drug therapy must be maintained and be available to allow the rational prescription of additional drugs and the review of all drug therapy at each patient-doctor contact. Further studies of other well-recognized drug interactions are required in the community to indicate the relevance and clinical importance to doctors who prescribe drugs of the formidable lists of substances which interact, such as the 410 pages of tables recently compiled by Martin (1971). Possibly the inappropriate prescription of fixed doses of a drug to patients in whom wide differences in the absorption, distribution, metabolism, and excretion of the drug may occur may be as important, if not more so, than drug interactions.

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Effect of Heparin on Renal Function in Patients With Oliguria

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Summary

The effect of short-term administration of heparin has been studied in seven patients with oliguric glomerulonephritis, five with accelerated hypertension, and three with transplant rejection. Measurements were made of the glomerular filtration rate, radiofibrinogen catabolism, and complement inhibition. Beneficial effects on fibrinogen catabolism were found in some cases of accelerated hypertension and transplant rejection, but heparin alone had no dramatic effect in glomerulonephritis. Heparin produced an increase of glomerular filtration rate, but in-vivo inhibition of complement by heparin was small.

Introduction

Platelet and fibrin deposits are found in the renal glomeruli of patients with rapidly progressive glomerulonephritis, malignant hypertension, and transplant rejection when such patients have oliguria. Persistence of fibrin may account in part for reduction of glomerular filtration. In the case of glomerulonephritis circulating immune complexes, when concentrated in the renal filters, damage platelets (Cochrane and Dixon, 1968) so that intraglomerular coagulation follows. The natural renal protective mechanisms are its endothelial cell fibrinolytic potential (Holemans *et al.*, 1965; Holemans *et al.*, 1967), resulting in the production of small fibrin degradation products which themselves protect platelets from aggregation (Larrieu *et al.*, 1967) and immune damage (Salmon and Lambert, 1971), and the phagocytic capacity for fibrin and immune complexes of the mesangial and endothelial cells (Vassalli and McCluskey, 1965).

Similar platelet deposition and coagulation is a feature of certain types of transplant rejection (Porter, 1967; Burrows *et al.*, 1970). In malignant hypertension it is likely that the high intravascular tension, leading to fibrin insudation through arteriolar walls, also damages endothelial cells (Wardle, 1971), which even in arteries do have some fibrinolytic activity (Onoyama and Tanaka, 1969). Platelet adhesion may follow, possibly because of exposure to subendothelial collagen and acid mucopolysaccharides (Murase *et al.*, 1971). Indeed, the proliferative response that is seen in the glomeruli in malignant hypertension is probably due exclusively to fibrin deposition (Ben-Ishay, 1967).

Kincaid-Smith *et al.* (1968) reported that heparin given as part of a regimen that included corticosteroids and immunosuppressive drugs greatly improved the urine output of six cases of "irreversible" acute renal failure due to glomerulonephritis. Such a measure is a logical extension of the use of heparin in experimental nephritis to prevent glomerular sclerosis (Silfverskiold, 1940; Kleinerman, 1954). Other groups have likewise reported the favourable effects of heparin on the course of glomerulonephritis (Shires *et al.*, 1966; Conte *et al.*, 1970; Cade *et al.*, 1971) and transplant rejection (McMillan, 1968; MacDonald *et al.*, 1970). The bad prognosis of anuric glomerulonephritis is well known (Merrill, 1957). Heparin has great potential in theory because it is not only the only effective antithrombin but it has also anti-inflammatory and anti-complementary actions (Ecker and Gross, 1929). Caution in the interpretation of results is necessary because heparin has a diuretic action (Majoor *et al.*, 1960) due to antagonism of the renin-angiotensin-aldosterone system (Schlatmann *et al.*, 1964). Moreover, control of heparin therapy can present special difficulties in the uraemic patient (Pitney *et al.*, 1970), in whom there is not only hypercoagulability and heparin resistance but also a metabolic platelet defect.

We report here the results of a study of the effect of heparin on renal function in 15 patients with oliguria or declining renal function due to glomerulonephritis, malignant hypertension, or transplant rejection which was monitored by measurement of the true glomerular filtration rate, by serial estimation of ⁵¹Cr-ethetic acid clearance, and by studies of radiofibrinogen cata-

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bolism. Similar studies were also made on 12 patients who did not receive heparin but who did receive standard treatments.

Patients and Methods

All patients were studied under steady-state conditions, receiving through the course of the study unaltered doses of immunosuppressant drugs, hypotensive agents, or diuretics. The 15 patients who were successfully heparinized without complication included five with accelerated hypertension who were also receiving hypotensive therapy, seven with chronic or progressive proliferative glomerulonephritis who received heparin as their only treatment, and three with renal transplant rejection who were receiving immunosuppressants as well as heparin. Twelve other patients underwent the same investigations and received standard treatments but no heparin. They included seven transplant patients, three with accelerated hypertension, and two with proliferative glomerulonephritis; they cannot be regarded strictly as control patients. In all there were six patients with chronic proliferative glomerulonephritis in the study, four heparinized and two control, and three patients with rapidly progressive glomerulonephritis all of whom were heparinized.

Informed permission was obtained for each study. After thyroid blockade with 150 mg of sodium iodide had been given intravenously 50 μ Ci of 125 I-labelled fibrinogen (Radio Pharmaceuticals, Amersham) was injected, combined in six cases with 30 μ Ci of free sterile 131 I-iodide. The double isotope technique allows a correction to be made for impaired iodide excretion from the body water in patients with reduced glomerular filtration (Donato *et al.*, 1967). The activity of the plasma sample taken at 15 minutes was used to calculate the plasma volume. Thereafter plasma samples were collected six-hourly for 48 hours and then twice daily for up to 10 days. Sodium iodide solution was given by mouth twice daily for three weeks in order to ensure thyroid blockade and urinary excretion of the isotopic iodide. In each plasma sample the activities of the separated fibrinogen (125 I) and of the free radioiodide (131 I and 125 I) were counted. Plasma fibrinogen was also measured in each sample by the method of Ratnoff and Menzie (1951).

Urine collections were made quantitatively for each 24 hours and used for isotope counting, as well as for estimation of endogenous creatinine clearance and urinary sodium and potassium excretion. The body weight, plasma fibrinogen, and plasma volume being known, the intravascular fibrinogen pool could first be calculated. The fractional catabolic rate (F.C.R.) of the labelled fibrinogen, which is the percentage of the intravascular fibrinogen pool that is broken down each day, was calculated in three ways. Firstly, the plasma decay curve was resolved into its two exponential components according to the method of Matthews (1957). In so doing the percentage of the labelled fibrinogen that remained in the intravascular compartment was also obtained. Secondly, the amount of isotope excreted in the urine for each successive 24-hour period was divided by the mean 24-hour plasma activity for the day as described by Pearson *et al.* (1958). The third technique, based on the use of free 131 I-iodide injected together with the 125 I-fibrinogen, was also applied in order to correct for the diminished excretion of iodide in patients with impaired glomerular filtration (Donato *et al.*, 1967).

Determination of the glomerular filtration rate by the single-shot 51 Cr-ethetic acid clearance method (Chantler *et al.*, 1969) was performed on the third day of the fibrinogen study and again on the eighth day during the period of heparinization. Heparin was infused intravenously from the fifth day of the fibrinogen catabolism study, 10,000 units being given intravenously as the priming dose and at least 20,000 units/500 ml saline/12 hr as the maintenance dose. Heparin treatment was continued for at least four days. Clotting times were monitored with the Dale and Laidlaw coagulometer (Sharnoff and De Blasio, 1970) and the heparin dosage was adjusted to give a coagulation time of twice normal. Since patients with kidney disease show heparin

resistance, specimens of plasma were withdrawn during the period of heparinization for retrospective assay of the plasma heparin levels that were being achieved. The heparin assay was performed by the technique of Bassiouni (1953), based on the precipitation of heparin by a basic dye, azure A.

Similar specimens of serum from the patients with glomerulonephritis were taken before and during the period of heparinization for estimation of the degree of inhibition of haemolytic complement. The serial determinations of complement were made by the technique of Walton and Ellis (1958), using formalized sheep cells sensitized with six minimal haemolytic doses of haemolytic antibody and serial dilutions of the serum concerned up to 1/60. The dilution of serum that gave the 50% haemolysis end-point was calculated.

Results

The plan of the study and the response of Case 13 to heparin are shown in Fig. 1, and the changes that occurred as a result of heparinization or standard treatment are shown in Fig. 2. For a control group of 16 normal subjects the mean half-life of the 125 I-fibrinogen was 95.3 ± 10.9 hours, which gave an F.C.R. of $21.8 \pm 4.7\%$ of the intravascular fibrinogen pool. The proportion of the fibrinogen that stayed in the plasma was $82.5 \pm 7.0\%$. The first seven heparinized patients were those whose main problem was accelerated hypertension, including two with glomerulonephritis. Fibrinogen catabolism was normal

FIG. 1—Case 13. General plan of study and response of fibrinogen catabolic rate to heparinization. During period the F.C.R. fell from 46.0 to 15.6% and the 51 Cr-ethetic acid glomerular filtration rate rose from 16.8 to 21.0 ml/min. $t_{1/2}$ = Half-life of 125 I-fibrinogen in hours.

FIG. 2—Changes (or absence of change) in fibrinogen half-life (solid dots) and in 51 Cr-ethetic acid glomerular filtration rate (open circles) in patients who were heparinized and those who were not. In each case a favourable trend is upwards on the scale. Encircled dots refer to three patients with rapidly progressive glomerulonephritis.

in those (Cases 1, 5, and 6) who had already responded well to hypotensive therapy but distinctly abnormal in those who were not responding. One patient (Case 3) with microangiopathic haemolytic anaemia had a greatly accelerated fibrinogen catabolic rate, with a half-life of 62.5 hours, that was unchanged by heparin even in a dose of 60,000 units/day. Indeed, this patient's hypertension and accelerated fibrinogen catabolism were checked only by subsequent bilateral nephrectomy. On the other hand, two patients (Cases 2 and 4) showed amelioration of their enhanced fibrinogen catabolism during the course of heparinization. Thus the fibrinogen half-life in Case 2 changed from 40 to 75 hours (F.C.R. 63.8% → 32.0%) and in Case 4 from 50 to 107 hours (F.C.R. 41.2% → 19.2%). In addition the fibrinogen half-life in Case 5, which would have been accepted as being in the normal range at 90 hours, nevertheless changed to 104 hours under the effect of heparin (F.C.R. 29.6% → 25.6%).

Among the patients with glomerulonephritis (Cases 6-12) three had increased fibrinogen catabolism, although all three had also some degree of hypertension. In none of the glomerulonephritis patients was there any response of the fibrinogen catabolic rate to heparinization in spite of the fact that subsequent assay showed them to have mean plasma heparin levels in the range 0.05-0.15 mg/ml. As for the transplant patients, two (Cases 13 and 14) of the three who were heparinized showed amelioration of fibrinogen catabolism in response to the heparin (see Fig. 1). It is to be noted also that these transplant patients showed increased fibrinogen catabolic rates.

Reference to the ^{51}Cr -edetic acid glomerular filtration rate data, which are given in Fig. 2, shows, firstly, that the groups were not equally matched, because initially low filtration rates below 20 ml/min were present in two-thirds of the 15 patients in the heparinized group, whereas only five of the 12 patients who were not heparinized had low filtration rates. The seemingly better prognosis of the non-heparinized group must be borne in mind in relation to the results obtained. Since the error of duplicate estimations of ^{51}Cr -edetic acid clearance was found to be 7.0%, an increase in glomerular filtration rate of over 10% has been regarded as significant. The number of patients with an increase in glomerular filtration rate by this criterion in each group is shown in Table I. The numbers do not attain statistical significance, but by combination of the more favourable responses in the hypertension and transplant groups, using Kimball's (1954) partition, $\chi^2 = 3.4$ (for 1 D.F. $P < 0.1$), which is significant.

The results obtained when increases in glomerular filtration rate were expressed as absolute values are shown in Table II. It is clear that the mean percentage increase in glomerular filtration rate was greater in the patients receiving heparin. If it is borne in mind that the patients in the heparinized group started with lower filtration rates, the results indicate that heparinization is at least as good as other forms of therapy.

TABLE I—Numbers of Patients with Increase in Glomerular Filtration Rate of Over 10%

	Hypertension	Glomerulonephritis	Transplant Rejection
Heparinized patients	3/5	4/7	3/3
Patients on standard treatment	0/3	1/2	3/7
	$\chi^2 = 2.88$		$\chi^2 = 2.85$

TABLE II—Mean Absolute Increases in Glomerular Filtration Rate (ml/min). Numbers of Patients are given in Parentheses

	Hypertension	Glomerulonephritis	Transplant Rejection
Heparinized patients	36.3 ± 10.8 (5)	30.9 ± 16.3 (7)	26.8 ± 2.8 (3)
Patients on standard treatment	18.3 ± 7.5 (3)	10.6 ± 4.2 (2)	14.6 ± 29.8 (7)
	$t = 2.2, 6 \text{ d.f.}$ $P < 0.1$	$t = 1.54, 7 \text{ d.f.}$ $P < 0.2$	

TABLE III—Mean Changes recorded in the Two Groups of Patients

	Change in ^{51}Cr -edetic acid Clearance (%)	Change in Endogenous Creatinine Clearance (%)	Change in Sodium Excretion (%)	Change in Potassium Excretion (%)	Change in Urine Volume (%)
Heparinized patients (n = 15)	+29.2	+13.6	+12.3	-6.3	+13.3
Non-heparinized patients (n = 12)	+12.1	+10.6	+26.7	+21.4	+33.1

The mean percentage differences in the values studied are summarized in Table III. The favourable increase in ^{51}Cr -edetic acid clearance in the heparinized group is apparent, but at first sight the less impressive change in endogenous creatinine clearance is disappointing. It should be remembered, however, that ^{51}Cr -edetic acid clearance has been shown to give a better estimate of the glomerular filtration rate than creatinine clearance in patients suffering from proteinuria and advanced renal failure (Favre and Wing, 1968) and that its reproducibility is better (Chantler *et al.*, 1969). Glomerular filtration rate determinations from creatinine or inulin clearance can vary by 20% (Bennett and Porter, 1971) but variance in ^{51}Cr -edetic acid estimations has been estimated at only 4.7% (Francois *et al.*, 1971). Nor does ^{51}Cr -edetic acid clearance suffer from errors in urine collection in ill patients. Also of note is the fact that patients on heparin had evidence of slight potassium retention due to aldosterone antagonism, whereas in the standard treatment group there was potassium loss.

Serum samples from the patients with glomerulonephritis were used for haemolytic complement assays, and the data are recorded in Fig. 3 in relation to the corresponding plasma heparin levels so as to give an indication of the dose of heparin

FIG. 3—Inhibition of haemolytic complement produced by heparin in vivo with comparable in-vitro amounts.

required for complement inhibition in-vivo. Levels of heparin as high as 15 units/ml resulted in only some 25% inhibition of haemolytic complement, and levels of heparin had to be of the order of 10-15 units/ml to produce any inhibition at all.

Discussion

There have been several reports of the effect of heparinization on the course of patients with renal disease (Kincaid-Smith *et al.*, 1968; Conte *et al.*, 1970; Freedman *et al.*, 1970; Herdman *et al.*, 1970; Cade *et al.*, 1971; Arieff and Pingerra, 1972) but no study so far has taken account of the weak diuretic action of heparin by coincident measurement of glomerular filtration rates. We have attempted to assess the value of heparin critically over a short period of intensive treatment by direct measurement of glomerular filtration, by studying its effect on radiofibrinogen catabolism, and by estimating its potential for inhibition of complement.

The results show that under conditions of optimal hepariniza-

tion the ^{51}Cr -edetic acid glomerular filtration rate was increased by a mean of 29%. In the group on standard forms of therapy the mean increase was only 12.1%. Moreover, it has already been emphasized that the latter group started with better filtration rates. It is concluded that optimal heparinization exerts a beneficial effect over and above those of other forms of therapy but, as shown in Tables I-III, with the relatively small groups of patients involved statistical significance was only just achieved. It must also be recognized that the slope technique for analysis of ^{51}Cr -edetic acid clearance is at a disadvantage in patients in renal failure with unknown abnormalities of body water.

The action of heparin was to increase the output of sodium while causing reabsorption of potassium. This is consistent with its recorded action as a diuretic with aldosterone antagonism (Majoor *et al.*, 1960; Schlattman *et al.*, 1964). The minimum effective dose for such action is said to be 30,000 units/day. The characteristic delay in the natriuresis for 24-48 hours was also noted in this study.

It is presumed that heparin increased the glomerular filtration rate by lessening the tendency to glomerular fibrin deposition in accelerated hypertension and progressive glomerulonephritis and after receipt of a renal allograft. There were indeed three patients with accelerated hypertension who also had accelerated fibrinogen catabolism which was ameliorated under the influence of heparin. Administration of heparin in the course of a radio-fibrinogen study is the accepted way of demonstrating the presence of intravascular coagulation. Undoubtedly a high intravascular pressure, in causing vascular damage, triggers fibrin deposition, especially in the kidney (Wardle, 1971). That the primary therapeutic aim is to lower the blood pressure is emphasized by one hypertensive patient (Case 3) whose intravascular coagulation could not be arrested by large doses of heparin but who subsequently responded after bilateral nephrectomy. Heparin resistance in this patient could have been due to the release of large amounts of coagulant platelet factor 4 by the microangiopathic process (Niewiarowski *et al.*, 1968). A point about heparin that deserves serious consideration is that it may well be used to combat the decline of renal function that is often seen after therapeutic reduction of the blood pressure in accelerated hypertension (Woods and Blythe, 1967) and that at this stage its action as an aldosterone antagonist may be beneficial.

Two of the three transplant patients also showed reduction of their accelerated fibrinogen catabolic rate with heparin, and in Case 13 (Fig. 1) the process was reversible and quite dramatic. This patient was at the time under treatment for late rejection which clearly involved a vascular process, although no microangiopathic red cell changes were discernible. At the time serum levels of fibrin degradation products were slightly increased. It has been our general experience that fibrinogen catabolic rates are increased, owing in part to intravascular coagulation for up to three weeks after receipt of a renal allograft, but this is the subject of a separate communication.

It is of interest and disappointing to note that none of the five patients with proliferative glomerulonephritis with oliguria, included three with "rapidly progressive glomerulonephritis," showed any response of the increased fibrinogen catabolic rate to heparin. These patients were not, however, receiving any other form of immunosuppression, nor was heparinization pushed to the limit at which bleeding might occur. This result can be contrasted with the recent observations of Arieff and Pingerra (1972), who produced a good increase in creatinine clearance by the combined use of prednisone, immunosuppressive drugs, and heparin followed by warfarin. They suggested that prednisone acts synergistically with heparin.

In addition, we can now report that the degree of inhibition of haemolytic complement that can be achieved by heparinization is disappointingly small, of the order of 10-20%. The discrepancy between the action of heparin on complement in vitro and in vivo cannot be explained here. Antiheparins in the plasma in chronic renal disease may play some part. Garrotty (1972),

who assessed the effect of heparin on complement with respect to the detection of blood group antibodies, also found that the heparin concentration should be at least 10 units/ml to exert any effect.

In conclusion, it appears that heparin does produce an increase in the glomerular filtration rate in these conditions. During the course of accelerated hypertension a case can be presented for heparinization once the blood pressure has been reduced to safe levels. Heparin also has a beneficial effect in renal transplant rejection with superimposed vascular changes. In glomerulonephritis heparin alone has no dramatic effect but may be useful as an adjunct to immunosuppressive therapy. Heparinization should be undertaken only when there are facilities for day and night control and only after the blood pressure has been controlled.

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